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(54) Title: QUINAZOLINES AS MMP-13 INHIBITORS

(57) Abstract: A compound selected from those of formula (I): in which: R<sub>1</sub> represents a group selected from hydrogen, amino, alkyl, alkenyl, aminoalkyl, aryl, arylalkyl, heterocycle, and cycloalkylalkyl, optionally substituted, W represents oxygen, sulphur, or =N-R', in which R' is as defined in the description, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> represent nitrogen or -C-R<sub>6</sub> in which R<sub>6</sub> is as defined in the description, Y represents oxygen, sulphur, -NH, or -N(C<sub>1</sub>-C<sub>6</sub>)alkyl, Z represents oxygen, sulphur, -NR<sub>7</sub> in which R<sub>7</sub> is as defined in the description, and optionally carbon atom, n is an integer from 1 to 8 inclusive, Z<sub>1</sub> represents -CR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub> are as defined in the description, A represents aromatic or non-aromatic, heterocyclic or non-heterocyclic ring system, m is an integer from 0 to 7 inclusive, the group(s) R<sub>2</sub> is (are) is as defined in the description, R<sub>3</sub> represents hydrogen, alkyl, alkenyl, alkynyl, or a group of formula: in which Z<sub>2</sub>, B, R<sub>5</sub>, P and q are as defined in the description, optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof, and medicinal products containing the same are useful as specific inhibitors of type-13 matrix metalloprotease.

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**QUINAZOLINES AS MMP-13 INHIBITORS****Field of the invention.**

The present invention relates to novel substituted quinazolines which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular  
5 for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

**Technological background of the invention.**

Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the  
10 destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

15 Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is  
20 the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the  
25 membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

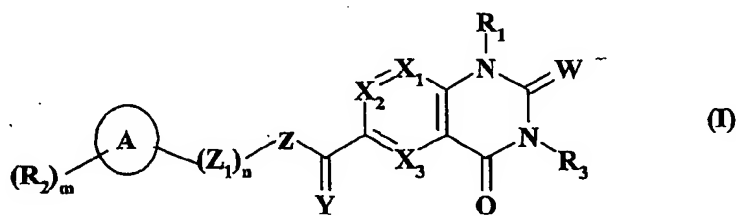
There is a need in the prior art for novel MMP inhibitors, more particularly for MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating pathologies associated with the destruction of the extracellular matrix and with cancer.

### Summary of the invention

The invention relates to a substituted quinazoline of formula (I):



in which:

$R_1$  represents a group selected from :

- hydrogen, amino,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, mono $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, di $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, aryl, aryl $(C_1-C_6)$ alkyl, heterocycle, and 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino,  $(C_1-C_6)$ alkyl, cyano, halo $(C_1-C_6)$ alkyl,  $C(=O)OR_4$ ,  $OR_4$  and  $SR_4$ , in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl,



W represents an oxygen atom, a sulphur atom, or a group  $=N-R'$ , in which  $R'$  represents  $(C_1-C_6)$ alkyl, hydroxyl, or cyano,

$X_1$ ,  $X_2$  and  $X_3$  represent, independently of each other, a nitrogen atom or a group  $-C-R_6$  in which  $R_6$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino, hydroxyl,  $(C_1-C_6)$ alkoxy, and halogen,  
5 with the proviso that not more than two of the groups  $X_1$ ,  $X_2$  and  $X_3$  simultaneously represent a nitrogen atom,

Y represents a group selected from oxygen atom, sulphur atom,  $-NH$ , and  $-N(C_1-C_6)$ alkyl,

Z represents:

- 10
- an oxygen atom, a sulphur atom,
  - or a group  $-NR_7$  in which  $R_7$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl, and heteroaryl, and
  - when Y is an oxygen atom, a sulphur atom, or a group  $-N(C_1-C_6)$ alkyl, Z optionally represents a carbon atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl, an aryl,

15 an aryl $(C_1-C_6)$ alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

$Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  and  $R_9$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, halo $(C_1-C_6)$ alkyl, halogen, amino,  $OR_4$ ,  $SR_4$  or  $C(=O)OR_4$  in which  $R_4$  represents a hydrogen or  $(C_1-C_6)$ alkyl, and

- 20
- when n is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,

• and when one of the carbon atoms in the hydrocarbon chain  $Z_1$  is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group  $-C(=Y)-Z-$  optionally may be absent in the general formula (I),

A represents a group selected from :

- 5      • aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

10      m is an integer from 0 to 7 inclusive,

the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen,  $-CN$ ,  $NO_2$ ,  $SCF_3$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SOR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- 15      •  $X_5$  represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or  $(C_1-C_6)$ alkyl,

        • k is an integer from 0 to 3 inclusive,

        •  $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

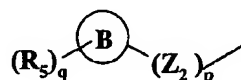
- 20      •  $X_4$  represents a group selected from single bond,  $-CH_2-$ , oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or  $(C_1-C_6)$ alkyl group,

        •  $R_{12}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which

may be identical or different, selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

R<sub>3</sub> represents a group selected from:

- 5       • hydrogen,
- (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, (C<sub>3</sub>-C<sub>6</sub>)alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, -C(=O)NR<sub>10</sub>R<sub>11</sub>, -C(=O)OR<sub>10</sub>, OR<sub>10</sub>, and SR<sub>10</sub>, in which R<sub>10</sub> and R<sub>11</sub>, which may be identical or different, represent hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 10       • and the group of formula :

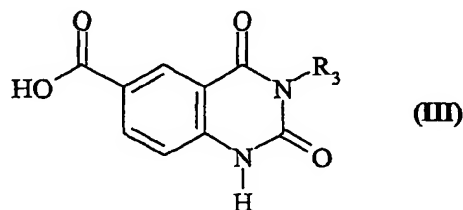


- ✓ in which p is an integer from 0 to 8 inclusive,
- ✓ Z<sub>2</sub> represents -CR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub>, independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, amino, OR<sub>4</sub>, SR<sub>4</sub> and -C(=O)OR<sub>4</sub> in which R<sub>4</sub> represents hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and
- 15       • when p is greater than or equal to 2, the hydrocarbon chain Z<sub>2</sub> optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z<sub>2</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl, or a carbonyl group,
- 20       • B represents a group selected from:
  - 25       • an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and

- a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- ✓ q is an integer from 0 to 7 inclusive,
- 5 ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{18}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-R_{19}-C(=O)OR_{15}$ ,  $-X_6-R_{20}$ , and  $-C(=O)-R_{21}-NR_{15}R_{16}$  in which :
- 10 -  $X_7$  represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a  $(C_1-C_6)$ alkyl group,
- 15 - k is an integer from 0 to 3 inclusive,
- $k_1$  is an integer from 0 to 2 inclusive,
- $k_2$  is an integer from 1 to 4 inclusive,
- $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
- 20 -  $R_{18}$  represents a group selected from  $(C_1-C_6)$ alkyl,  $-R_{21}-NR_{15}R_{16}$ ,  $-R_{21}-NR_{15}-C(=O)-R_{21}-NR_{16}R_{17}$ , and  $-C(=O)O-R_{21}-NR_{15}R_{16}$  in which  $R_{21}$  represents a linear or branched  $(C_1-C_6)$ alkylene group, and  $R_{15}$ ,  $R_{16}$  and  $R_{17}$  are as defined hereinbefore,

- $R_{19}$  represents a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group,
- $X_6$  represents a group selected from single bond, -CH<sub>2</sub>-, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- 5        -  $R_{20}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and -C(=O)OR<sub>4</sub> wherein R<sub>4</sub> represents hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4  
10        heteroatoms selected from nitrogen, oxygen and sulphur,  
with the proviso that when X<sub>1</sub> represents a nitrogen atom, X<sub>2</sub> cannot represent a carbon atom substituted with a methyl group or with NH-CH<sub>3</sub>,  
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.
- 15        The compounds of the present invention are useful as inhibitors, in particular as selective inhibitors, of the enzyme matrix metalloprotease-13 (MMP-13).

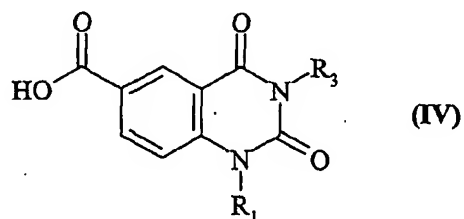
The invention also relates to compounds used mainly as intermediates for the synthesis of the compounds of formula (I). These intermediate compounds have the general formula (III) below:



20

in which R<sub>3</sub> has the same meaning as defined for the compound of formula (I).

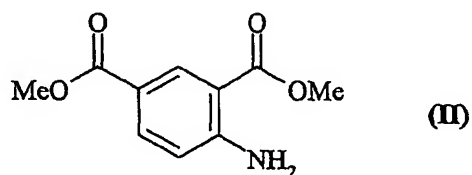
The invention also relates to compounds used mainly as intermediates for the synthesis of the compound of formula (I), which have the general formula (IV) below:



in which  $R_1$  et  $R_3$  have the same meaning as for a compound of formula (I).

- 5 The invention also relates to a process for manufacturing the compound of formula (I) in which:
- $R_2$ ,  $R_3$ ,  $Z_1$ ,  $A$ ,  $n$  and  $m$  are as defined in the compound of general formula (I),
  - $X_1$ ,  $X_2$ ,  $X_3$  are each a group  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,
  - $Y$  is  $O$ ,
  - 10 -  $Z$  is  $-N-R_7$  in which  $R_7$  is as defined in the compound of general formula (I),
  - and  $W$  is  $O$ .

This process is characterized in that it comprises the reaction of a compound of formula (II):

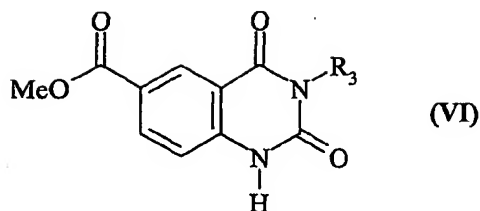


- 15 with pyridine and the compound of general formula (V):



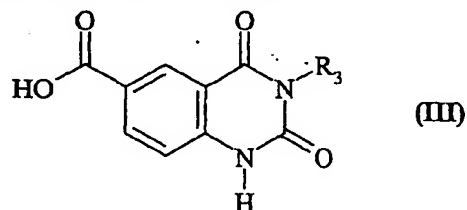
in which  $R_3$  is as defined above for the compound of formula (I),  
to give the compound of general formula (VI):

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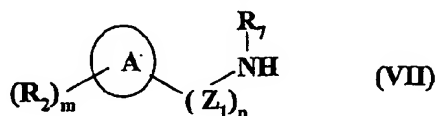
in which  $R_3$  is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which  $R_3$  is as defined above.



5

In a subsequent step of the synthetic process, the compound of general formula (III) obtained above is reacted, in the presence of an acid activator such as O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) with the compound of general formula (VII):

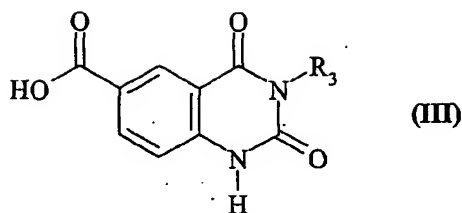


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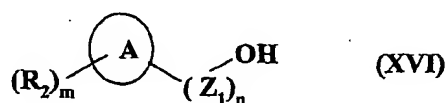
in which  $R_7$  is selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A,  $R_2$ ,  $Z_1$ , n and m are as defined above for the compound of formula (I), to give the compound of general formula (I) in which  $R_1$  represents hydrogen,  $X_1$ ,  $X_2$  and  $X_3$  are each  $-C-R_6$  in which  $R_6$  represents hydrogen atom, Y is O, Z is N- $R_7$ , W is O, , and A,  $R_2$ ,  $Z_1$ , n and m are as defined hereinbefore.

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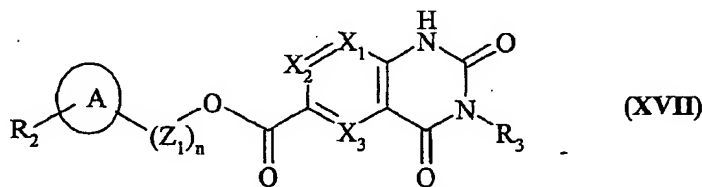
In particular, when W is O, Y is O and Z is O, the compounds of formula (I) corresponding to this definition may be obtained by reacting a compound of general formula (III):



in which  $R_3$  is as defined in the compound of general formula (I),  
with a compound of general formula (XVI):



- 5 in which  $Z_1$ ,  $A$ ,  $R_2$ ,  $n$  and  $m$  are as defined in the compound of general formula (I),  
to give a compound of general formula (XVII):



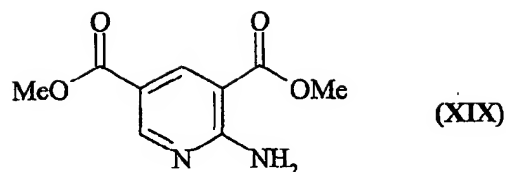
in which  $A$ ,  $R_2$ ,  $R_3$ ,  $Z_1$ ,  $m$  and  $n$  are as defined for the compound of general formula (I), and  
 $X_1$ ,  $X_2$ , and  $X_3$  are each  $-C-R_6$  in which  $R_6$  represents hydrogen atom,

- 10 followed by reacting the compound of formula (XVII), in presence of a base, with the  
compound of general formula (VIII),  $X-R_1$ , in which  $R_1$  is as defined for the compound of  
formula (I) and  $X$  is a leaving group such as halogen,  
to give the compound of general formula (I) in which  $X_1$ ,  $X_2$  and  $X_3$  are each  $-C-R_6$  in  
which  $R_6$  is as defined hereinbefore,  $W$  is  $O$ ,  $Y$  is  $O$ ,  $Z$  is  $O$ , and  $R_1$ ,  $R_2$ ,  $R_3$ ,  $Z_1$ ,  $A$ ,  $n$  and  $m$   
15 are as defined hereinbefore.

In particular, when  $X_2$  and  $X_3$  are each  $-C-R_6$  in which  $R_6$  represents hydrogen atom,  $X_1$  is  
 $N$ ,  $Z$  is  $O$  and  $Y$  is  $O$ , the compounds of formula (I) corresponding to this definition may be  
obtained by reacting a compound of general formula (XIX):

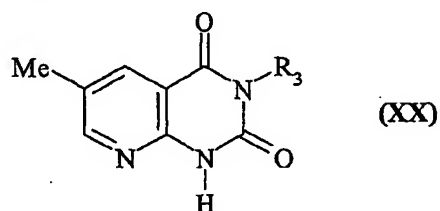


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with pyridine and a compound of general formula  $O=C=N-R_3$  (V) in which  $R_3$  is as defined in the compound of formula (I),

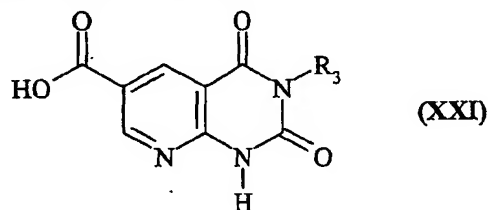
to give a compound of general formula (XX):



5

in which  $R_3$  is as defined hereinbefore,

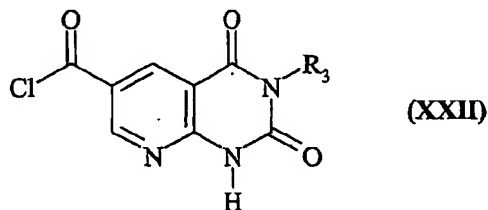
followed by reacting the compound of general formula (XX) in the presence of  $KMnO_4$  to give the compound of general formula (XXI):



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in which  $R_3$  is as defined hereinbefore,

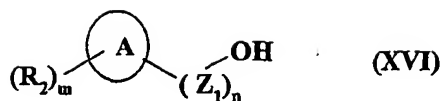
followed by reacting a compound of general formula (XXI) in the presence of  $SOCl_2$  and  $CHCl_3$  to give the compound of general formula (XXII):



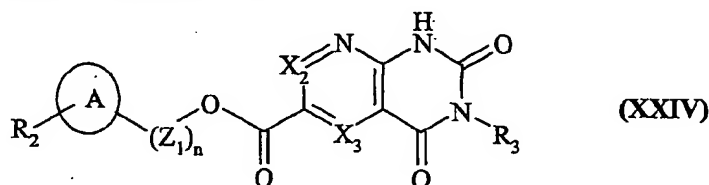
in which  $R_3$  is as defined hereinbefore,

15

followed by reacting the compound of formula (XXII) with the compound of general formula (XVI):



in which A, R<sub>2</sub>, Z<sub>1</sub>, n and m are as defined in the compound of formula (I),  
to give the compound of general formula (I):



- 5 in which A, R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, m and n are as defined hereinbefore, X<sub>2</sub> and X<sub>3</sub> are each -C-R<sub>6</sub> in which R<sub>6</sub> is as defined hereinbefore, and R<sub>3</sub> are as defined for the compound of general formula (I).

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient.

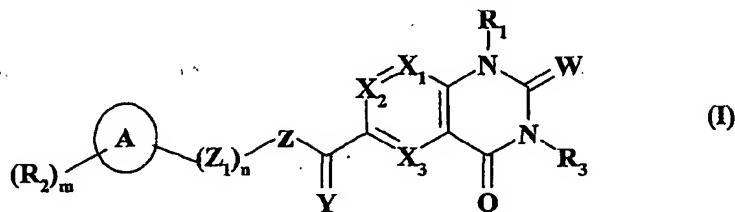
- 10 The invention also relates to the use of a compound of formula (I) for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease (MMP-13).

- 15 The invention also relates to a method for treating a disease or complaint involving a therapy by inhibition of matrix metalloprotease, and more particularly MMP-13, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient.

#### Detailed description of the invention

- 20 The Applicant has identified according to the invention novel compounds that are matrix metalloprotease inhibitors, and more specifically novel compounds that are MMP-13 inhibitors.

One subject of the invention is thus a substituted quinazoline of formula (I):



in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $W$ ,  $Y$ ,  $Z$ ,  $Z_1$ ,  $n$  and  $m$  are as defined hereinbefore in the compound of general formula (I),

- 5 optionally the racemic forms thereof, isomers forms thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

The invention relates particularly to the compounds of general formula (I) in which:

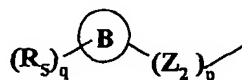
- $R_1$  represents hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl or 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl,
- 10 •  $W$  represents an oxygen atom or a sulphur atom,
- $X_1$  represents a nitrogen atom or  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,
- $X_2$  and  $X_3$  represent each  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,
- $Y$  represents an oxygen atom,
- $Z$  represents an oxygen atom or  $-NR_7$  in which  $R_7$  represents a hydrogen atom.

- 15 The invention also relates to the compounds of general formula (I) in which:

- $n$  is an integer from 1 to 6 inclusive,
- $Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  represents a hydrogen atom and  $R_9$  represents a hydrogen atom or a methyl group, and
- when  $n$  is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains a
- 20 double bond,
- or, one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, or a sulphur atom which is unsubstituted or substituted with one or two oxygens,

- A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, piperidyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,
  - m is an integer from 0 to 7 inclusive,
- 5     • the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, -CN,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:
- ✓  $X_5$  represents O, S or NH,
  - 10   ✓ k is an integer from 0 to 3 inclusive,
  - ✓  $R_{10}$  and  $R_{11}$ , identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
  - ✓  $X_4$  represents  $-CH_2-$ , or an oxygen atom,
  - ✓  $R_{12}$  represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen,
  - 15   hydroxyl and amino.

The invention also relates to the compounds of general formula (I) in which  $R_3$  represents hydrogen,  $(C_1-C_6)$ alkyl or the group of formula:



- ✓ in which p is an integer from 0 to 3 inclusive,
- 20   ✓  $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen, methyl, or phenyl, and
- when p is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one double bond,

- or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl, or a carbonyl group,
- 5    ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- ✓ q is an integer from 0 to 3 inclusive,
- ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from
- 10     $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-(CH_2)_kC(=O)NR_{15}R_{16}$  in which :
- 15    •  $X_7$  is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- $k_1$  is an integer from 0 to 2 inclusive,
- $k_2$  is an integer from 1 to 4 inclusive,
- $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
- 20    The invention relates more particularly to the compounds of general formula (I) in which:  
 $R_1$  represents a group selected from:
- hydrogen, amino,
  - $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, mono $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, di $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, aryl, aryl $(C_1-C_6)$ alkyl, heterocycle, and 3- to
- 25    6-membered cycloalkyl $(C_1-C_6)$ alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino,  $(C_1-$

C<sub>6</sub>)alkyl, cyano, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, C(=O)OR<sub>4</sub>, OR<sub>4</sub> and SR<sub>4</sub>, in which R<sub>4</sub> represents hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl,

W represents an oxygen atom, a sulphur atom, or a group =N-R', in which R' represents (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxyl, or cyano,

- 5     X<sub>1</sub> represents a nitrogen atom or a group -C-R<sub>6</sub> in which R<sub>6</sub> represents hydrogen atom, X<sub>2</sub> and X<sub>3</sub> represent, independently of each other, a group -C-R<sub>6</sub> in which R<sub>6</sub> represents a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, amino, hydroxyl and halogen,

Y represents an oxygen atom,

- 10     Z represents an oxygen atom, or a group -NR<sub>7</sub> in which R<sub>7</sub> represents a group selected from hydrogen, and (C<sub>1</sub>-C<sub>6</sub>)alkyl,

n is an integer from 1 to 6 inclusive,

Z<sub>1</sub> represents -CR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub>, independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and hydroxyl, and

- 15     • when n is greater than or equal to 2, the hydrocarbon chain Z<sub>1</sub> optionally contains one or more multiple bonds,  
     • or one of the carbon atoms in the hydrocarbon chain Z<sub>1</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl,

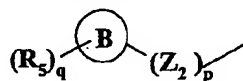
- 20     A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazo-lyl, and indolyl,

m is an integer from 0 to 3 inclusive,

the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- 5       •  $X_5$  represents O, S or  $NH$ ,
- $k$  is an integer from 0 to 3 inclusive,
- $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
- $X_4$  represents  $-CH_2-$ , or an oxygen atom,
- 10       •  $R_{12}$  represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

$R_3$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and the group of formula :



- ✓ in which  $p$  is an integer from 0 to 6 inclusive,
- 15   ✓  $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and hydroxy, and
  - when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one or more multiple bonds,
  - or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,
- 20   ✓  $B$  represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- 25   ✓  $q$  is an integer from 0 to 3 inclusive,

- ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-X_6-R_{20}$  in which :
- $X_7$  is S, O or NH,
  - $k$  is an integer from 0 to 3 inclusive,
  - $k_1$  is an integer from 0 to 2 inclusive,
  - $k_2$  is an integer from 1 to 4 inclusive,
  - $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
  - $X_6$  represents a single bond,  $-CH_2-$ , an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
  - $R_{20}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.
- The invention also relates to the compounds of general formula (I) in which:
- $R_1$  represents a group selected from hydrogen, mono $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, di $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, aryl, aryl $(C_1-C_6)$ alkyl, and 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl,
- $W$  represents an oxygen atom, or a sulphur atom,
- $X_1$  represents a nitrogen atom or a  $-CH$  group,
- $X_2$  and  $X_3$  represent a  $-CH$  group,



Y represents a group selected from oxygen atom, sulphur atom, -NH, and -N(C<sub>1</sub>-C<sub>6</sub>)alkyl,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

5 Z<sub>1</sub> represents -CR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub>, independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl and hydroxy, and

- when n is greater than or equal to 2, the hydrocarbon chain Z<sub>1</sub> optionally contains one double bond,
  - or one of the carbon atoms in the hydrocarbon chain Z<sub>1</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a -NH group,
- 10

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

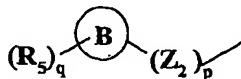
m is an integer from 0 to 3 inclusive,

15 the group(s) R<sub>2</sub>, which may be identical or different, is (are) selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -SO<sub>2</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, and -X<sub>4</sub>-R<sub>12</sub> in which:

- X<sub>5</sub> represents O, S or NH,
  - k is an integer from 0 to 3 inclusive,
  - R<sub>10</sub> and R<sub>11</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,
  - X<sub>4</sub> represents -CH<sub>2</sub>-, or an oxygen atom,
- 20

- $R_{12}$  represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

$R_3$  represents a group selected from methyl and the group of formula :



- 5 ✓ in which p is an integer from 0 to 3 inclusive,
- ✓  $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and hydroxy, and
  - when p is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one double bond,
- 10 • or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,
- ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl,
  - 15 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- ✓ q is an integer from 0 to 3 inclusive,
- ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from
  - 20  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-X_6-R_{20}$  in which :
    - $X_7$  is S, O or  $NH$ ,
  - 25 • k is an integer from 0 to 3 inclusive,
  - $k_1$  is an integer from 0 to 2 inclusive,
  - $k_2$  is an integer from 1 to 4 inclusive,

- $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
  - $X_6$  represents a single bond,  $-CH_2-$ , an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
  - 5     •  $R_{20}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.
- 10     The invention also relates to the compounds of general formula (I) in which:  
 $R_1$  represents hydrogen,  $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl, aryl $(C_1-C_6)$ alkyl, 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl,
- $W$  represents an oxygen atom,
- $X^1$  represents  $-CH$  group or nitrogen atom, and  $X^2$  and  $X^3$  represent each  $-CH$  group;
- 15      $Y$  represents an oxygen atom,
- $Z$  represents an oxygen atom or a  $-NH$  group,
- $n$  is an integer from 1 to 3 inclusive,
- $Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  and  $R_9$ , independently of each other, represent a group selected from hydrogen and methyl, and
- 20     • when  $n$  is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a  $-NH$  group,

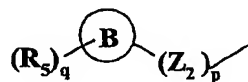
A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

m is an integer from 0 to 3 inclusive,

the group(s) R<sub>2</sub>, which may be identical or different, is (are) selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -SO<sub>2</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>,  
 5 -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, and  
 -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, in which:

- X<sub>5</sub> represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- 10 • R<sub>10</sub> and R<sub>11</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,

R<sub>3</sub> represents the group of formula :



- ✓ in which p is an integer from 0 to 3 inclusive,
- 15 ✓ Z<sub>2</sub> represents -CR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub>, independently of each other, represent a group selected from hydrogen, and methyl, and
  - when p is greater than or equal to 2, the hydrocarbon chain Z<sub>2</sub> optionally contains one double bond,
  - or one of the carbon atoms in the hydrocarbon chain Z<sub>2</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 20 ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,
- 25 ✓ q is an integer from 0 to 3 inclusive,

- ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , in which :
- $X_7$  is S, O or NH,
  - $k$  is an integer from 0 to 3 inclusive,
  - $k1$  is an integer from 0 to 2 inclusive,
  - $k2$  is an integer from 1 to 4 inclusive,
  - $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl.

The invention also relates to the compounds of general formula (I) in which  $R_1$  represents a hydrogen atom or a  $(C_1-C_6)$ alkyl group.

- 15 The invention also relates to the compounds of general formula (I) in which W represents an oxygen atom, Y represents an oxygen atom, Z represents a NH group,  $Z_1$  represents a methylene group, and  $n$  is equal to one.

The invention also relates to the compounds of general formula (I) in which  $X_1$  represents a -CH group or a nitrogen atom, and  $X_2$  and  $X_3$  represent each a -CH group.

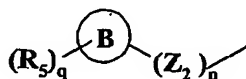
- 20 The invention also relates to the compounds of general formula (I) in which  $X_1$  and  $X_3$  represent each a -CH group, and  $X_2$  represents a -CH group or a nitrogen atom.

The invention also relates to the compounds of general formula (I) in which  $X_1$  and  $X_3$  represent each a -CH group, and  $X_2$  represents a nitrogen atom.

- 25 The invention also relates to the compounds of general formula (I) in which A represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl and benzofurazanyl,  $m$  is equal to

0 or 1, and  $R_2$  represents a group selected from  $(C_1-C_6)$ alkoxy, hydroxy, halogen, and  $(C_1-C_6)$ thioalkoxy.

The invention also relates to the compounds of general formula (I) in which  $R_3$  represents a group of formula :



in which:

$p$  is equal to one,

$Z_2$  represents a methylen group,

$B$  represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

$q$  is an integer from 0 and 2 inclusive,

and  $R_5$  represents a group selected from halogen, CN,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-S(O)_{k1}R_{15}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-X_6-R_{20}$  and  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , in which :

$k$  is an integer from 0 to 1 inclusive,

$k1$  is an integer from 0 to 2 inclusive,

$R_{15}$  and  $R_{16}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

$X_6$  represents a single bond,

$R_{20}$  represents a 5-membered heterocyclic ring comprising from 3 to 4 heteroatoms selected from oxygen and nitrogen and optionally substituted by a methyl group or an oxo group.

Among the groups defined above, the following substituents are particularly preferred:

- halogen: F, Cl, Br, I, preferably F, Br and Cl;

-  $(C_1-C_6)$ alkyl: linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms;

-  $(C_1-C_6)$ alkoxy: linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms;

- (C<sub>3</sub>-C<sub>6</sub>)alkenyl: containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly allyl;
- (C<sub>3</sub>-C<sub>6</sub>)alkynyl: containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly propargyl;
- 5    - aryl: containing from 5 to 10 and preferably 5 or 6 carbon atoms;
- heteroaryl: aryl group interrupted with one or several hetero atom selected from nitrogen, oxygen and sulphur. The term "interrupted" means that the hetero atom can replace a carbon atom of the ring. Examples of such groups containing a heteroatom are, inter alia, thienyl, pyridyl, benzofurazanyl;
- 10   - heterocycle: an aromatic or non-aromatic, 5-or 6-membered monocycle comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.
- aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 4 carbon atoms;
- cycloalkyl: containing from 3 to 8 and preferably from 3 to 6 carbon atoms,
- 15   - cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 3 carbon atoms and the cycloalkyl contains from 3 to 6 carbon atoms.
- multiple bond represent a double bond or a triple bond.

Among the compounds of the present invention that are preferred are the compounds described below in Examples 1 to Example 227.

- 20   More particularly, the preferred compounds of the present invention are compound of formula (I) which are:
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-
  - 25   carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
  - 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
  - 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt
- Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate
- 5 - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 1-Methyl-2,4-dioxo-3-[4-(2*H*-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 10 - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
- 15 - 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 20 - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate
- 25 - 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 30 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid



- 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid
- 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 5 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-
- 10 tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 15 - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
- Benzo[1,3]dioxol-5-ylmethyl-3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 20 (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 25 - 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 30 (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 5 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 10 - 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 15 - 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 20 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 25 - 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid
- 30 - 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine

- 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 5 - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
- 10 - Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 15 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 20 - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetic acid
- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetic acid
- 25 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 30 - 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate
- 5 - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid
- 10 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt
- Example 164: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
- 15 - 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 20 - and 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in J. Pharm. Sci., 1977, vol. 66:1-19. However, the expression "pharmacologically acceptable salts of a compound of formula (I) with a basic function" means the addition salts of the compounds of formula (I) formed from non-toxic mineral or organic acids such as, for example, hydrobromic acid, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, acetic acid, succinic acid, tartaric acid, citric acid, maleic acid, hydroxymaleic acid, benzoic acid, fumaric acid, toluenesulphonic acid, isethionic acid and the like. The various quaternary ammonium salts of the compounds of formula (I) are also included in this category of

compounds of the invention. In addition, the expression "pharmacologically acceptable salts of a compound of formula (I) with an acid function" means the usual salts of the compounds of formula (I) formed from non-toxic mineral or organic bases such as, for example, the hydroxides of alkali metals and of alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

As mentioned above, the compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended in the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended during the treatment of any pathology in which a destruction of extracellular matrix tissue is involved, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and certain cancers.

#### **Selectivity of the compounds of formula (I) for the enzyme MMP-13**

Most of the matrix metalloprotease inhibitors described in the prior art are non-selective inhibitors, capable of simultaneously inhibiting several matrix metalloproteases. For example, compounds such as CGS-27.023A and AG-3340 (Montana and Baxter (2000)) inhibit both MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13, i.e. these compounds of the prior art inhibit MMPs of both collagenase, gelatinase and stromelysin type.

It has been shown according to the invention that compounds of general formula (I) are selective inhibitors of MMP-13. "Selective inhibitors of MMP-13" refers to a compound of formula (I) which have an  $IC_{50}$  for MMP-13 at least 5 times lower than the  $IC_{50}$  for a MMP distinct from MMP-13, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times, 100 times or 1000 times lower than the  $IC_{50}$  value for a MMP distinct from MMP-13.

A MMP distinct from MMP-13 refers preferably to a matrix metalloprotease selected from MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

In particular, it has been shown according to the invention that the compounds of general formula (I), and more particularly the family of compounds given as examples in the present description, have an  $IC_{50}$  value for the enzyme MMP-13 which is often 1 000 times lower than the value of their  $IC_{50}$  for other matrix metalloproteases, in particular MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

The result of this is that the compounds of general formula (I) according to the invention are particularly useful in the treatment of complaints mainly associated with a physiological imbalance between the MMP-13 enzymes and their natural tissue inhibitors.

#### PHARMACEUTICAL FORMULATION OF THE COMPOUNDS OF THE INVENTION

A subject of the present invention is also a pharmaceutical composition comprising a compound of general formula (I) as defined above and a pharmaceutically acceptable excipient.

The invention also relates to the use of a compound of general formula (I) as defined above for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly a disease or complaint involving therapy by inhibition of type-13 matrix metalloprotease (MMP-13) such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers.

The invention also relates to a method for treating a pathology associated with an imbalance in the activity of MMPs, and more specifically of MMP-13, the said method comprising a step during which a pharmaceutically effective amount of an MMP-inhibitor compound according to the invention, or a pharmaceutical composition containing this compound, is administered to a patient requiring such a treatment.

Among the various pathologies associated with an imbalance in MMP activity, an MMP-13-inhibitor compound of general formula (I) according to the invention is particularly useful for treating all pathologies brought about by a degradation of extracellular matrix tissue, and more particularly for treating rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancer.

In an entirely preferred manner, a compound of general formula (I) as defined according to the invention will be used, preferably to treat arthritis, osteoarthritis and rheumatoid arthritis.

The compounds of the invention are administered in the form of compositions that are suitable for the nature and gravity of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product which may be absorbed in one or more dosage intakes. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula I) and 40% to 99.5% by weight of pharmaceutically acceptable vehicle.

The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration. By way of example, the following pharmaceutical forms may be envisaged, although the list given below is not limiting:

**1) Forms for oral administration:**

Drinkable solutions, suspensions, sachets of powder for drinkable solution, sachets of powder for drinkable suspension, gastro-resistant gel capsules, sustained-release forms, emulsions, HPMR capsules or gel capsules, lyophilizates to be melted under the tongue.

**2) Forms for parenteral administration:**

**Intravenous route:**

Aqueous solutions, water/cosolvent solutions, solutions using one or more solubilizing agents, colloidal suspensions, emulsions, nanoparticulate suspensions which can be used for the injection of sustained-release forms, dispersed forms and liposomes.

**Subcutaneous/intramuscular route:**

- 5 In addition to the forms which can be used intravenously and which can also be used for the subcutaneous and intramuscular routes, other types of forms such as suspensions, dispersed forms, sustained-release gels and sustained-release implants may also be used.

**3) Forms for topical administration:**

- 10 Among the most common topical forms that are distinguished are creams, gels (aqueous phases gelled with polymers), patches, which are dressings to be stuck directly onto the skin and which can be used to treat dermatosis without percutaneous penetration of the active substance, sprays, emulsions and solutions.

**4) Forms for pulmonary administration**

- 15 Forms such as solutions for aerosols, powders for inhalers and other suitable forms are distinguished in this category.

**5) Forms for nasal administration:**

This especially relates herein to solutions for drops.

**6) Forms for rectal administration:**

Suppositories and gels will be selected, inter alia.

- 20 It is also possible to envisage using forms allowing the administration of ophthalmic solutions or allowing the vaginal administration of the active principle.
- Another important category of pharmaceutical form which may be used in the context of the present invention relates to forms for improving the solubility of the active principle. By way of example, it may be envisaged to use aqueous solutions of cyclodextrin, and
- 25 more particularly forms comprising hydroxypropyl- $\beta$ -cyclodextrin. A detailed review of this type of pharmaceutical form is presented in the article published under the reference

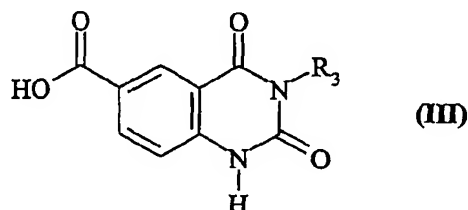


Journal of Pharmaceutical Sciences, 85 (11), 1142-1169 (1996), and incorporated into the present patent application by reference.

The various pharmaceutical forms recommended above are described in detail in the book "Pharmacie galénique" by A. Lehir (published by Masson, 1992 (6th edition)), which is  
5 incorporated into the present patent application by reference.

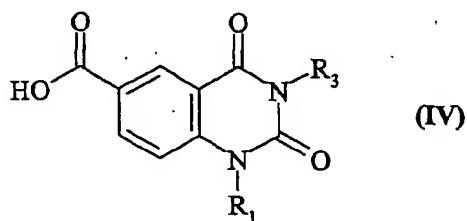
### INTERMEDIATE COMPOUNDS

The present invention also relates to an intermediate compound of general formula (III)



in which R<sup>3</sup> has the same meaning as for the compound of general formula (I).

10 According to another aspect, the present invention also relates to an intermediate compound of general formula (IV):



in which R<sub>1</sub> and R<sub>3</sub> have the same meaning as that defined above for the compound of general formula (I).

15 PROCESSES FOR SYNTHESIZING THE COMPOUNDS OF GENERAL FORMULA (I)

Throughout this application the following abbreviations have the meanings listed below:

DEAD: Diethyl azodicarboxylate

DIPEA: *N,N*-diisopropylethylamine

DMF: *N,N*-dimethylformamide

NMP: 1-methyl-2-pyrrolidinone

THF: tetrahydrofuran

TOTU: O-[(ethoxycarbonyl)cyanomethylenamino]-*N,N,N',N'*-tetramethyluronium

5 tetrafluoroborate

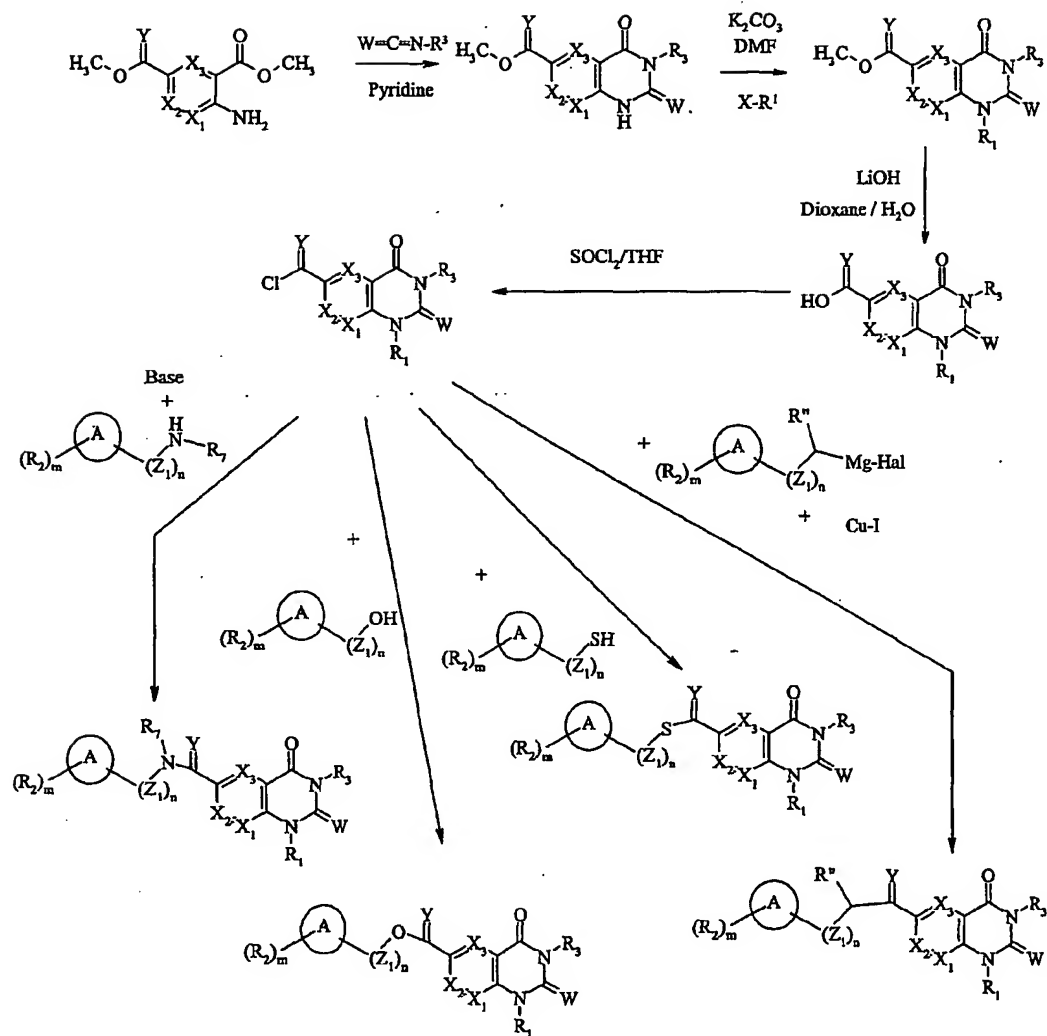
EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HOBt: 1-hydroxybenzotriazole hydrate

The compounds according to the present invention can be obtained by carrying out several synthetic processes. Some of these synthetic processes are described below:

10 **A) General process:**

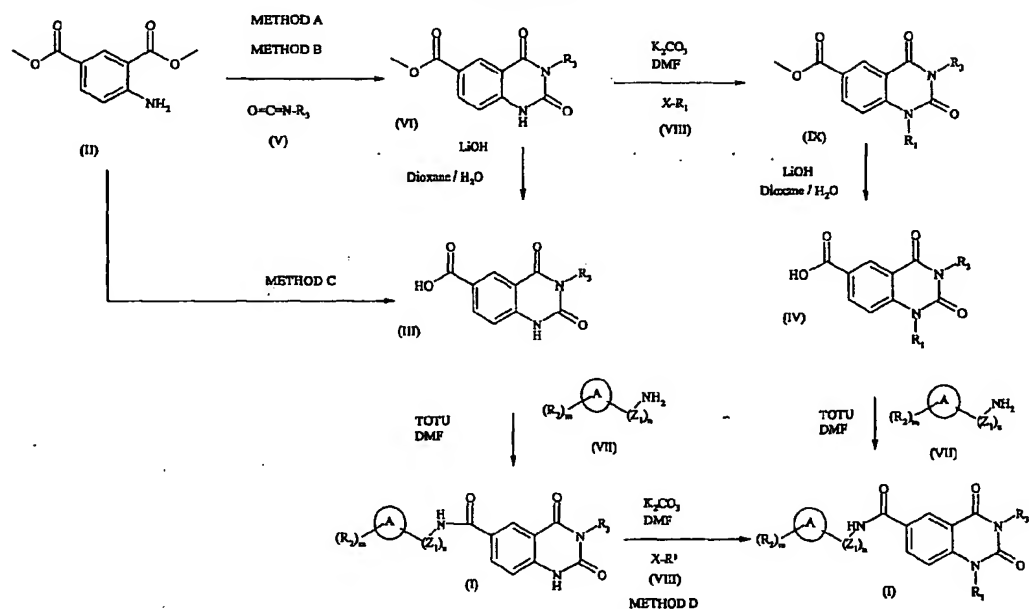
A general process for the synthesis of the compounds of general formula (I) is described in the following scheme:



in which  $\text{R}_7$  is hydrogen,  $(\text{C}_1-\text{C}_6)$ alkyl, aryl $(\text{C}_1-\text{C}_6)$ alkyl, cycloalkyl, aryl or heteroaryl,  $\text{R}''$  is  $(\text{C}_1-\text{C}_6)$ alkyl, aryl, aryl $(\text{C}_1-\text{C}_6)$ alkyl, aromatic or non-aromatic heterocycle or cycloalkyl, and  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{X}_1$ ,  $\text{X}_2$ ,  $\text{X}_3$ ,  $\text{A}$ ,  $\text{W}$ ,  $\text{Y}$ ,  $\text{Z}_1$ ,  $n$  and  $m$  have the same meaning as that defined above for the compound of formula (I).

**B) Synthetic process No. 1**

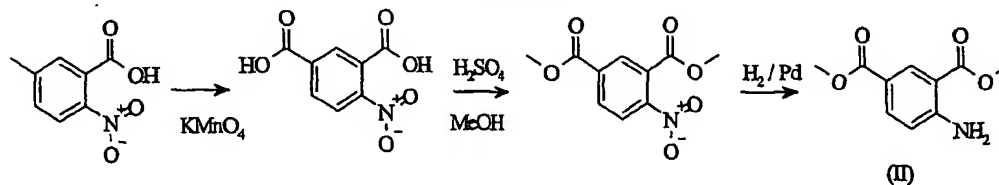
The compounds of the present invention may be obtained firstly by the method represented in Scheme 1 below.

**Scheme 1**

- 5 in which each of the generic substituents is as defined for the compound of general formula (I).

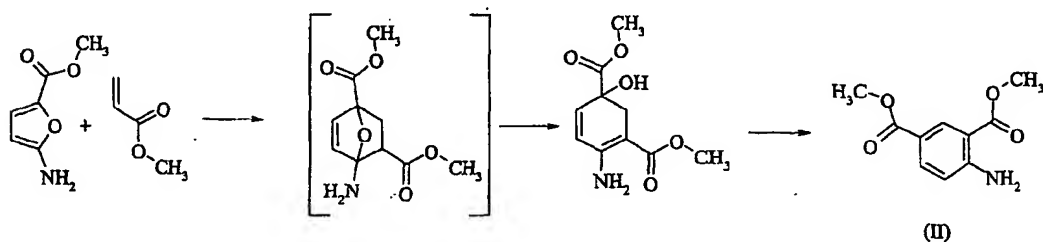
The intermediate compound of formula (II) which constitutes the starting material for the synthetic process illustrated by Scheme 1 above may be prepared in accordance with Scheme 2 below:

10

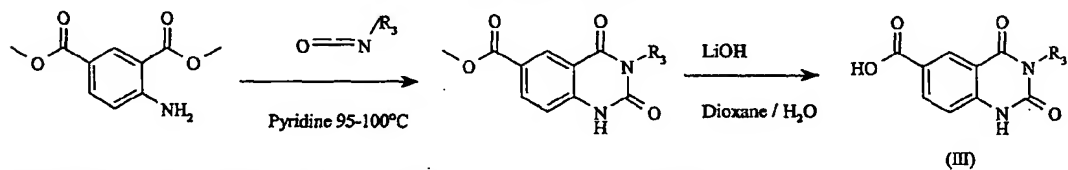
**Scheme 2**

The intermediate compound of formula (II) which constitutes the starting material in the process to synthesize the compounds of general formula (I) according to the invention as illustrated in Scheme 1 above may also be prepared according to the process illustrated in Scheme 3 below.

5

**Scheme 3**

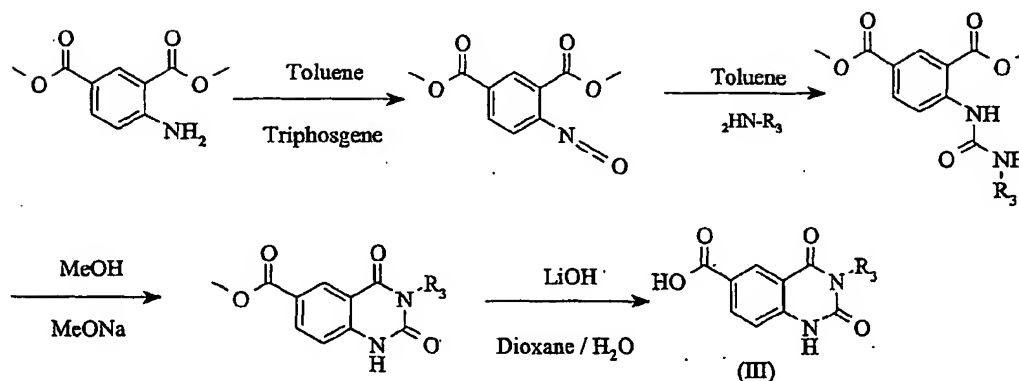
The compound of general formula (III) may be prepared, in accordance with the process described in Scheme 1 above, from the compound of formula (II), according to the synthetic Scheme 4 (Method A) below:

**Scheme 4 / Method A**

10

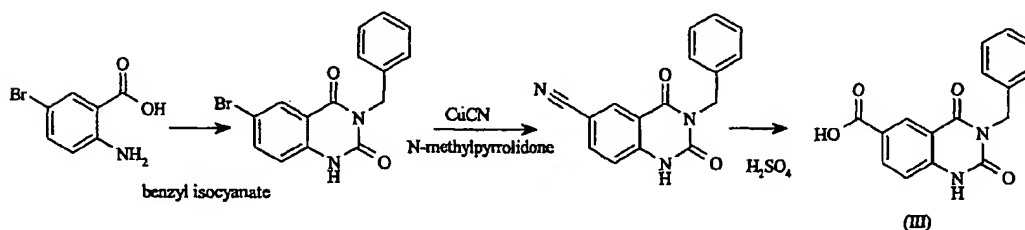
in which  $R_3$  is as defined above for the compound of general formula (I).

According to another aspect, the intermediate compound of formula (III) may be prepared, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method B, as illustrated in Synthetic Scheme 5 below:

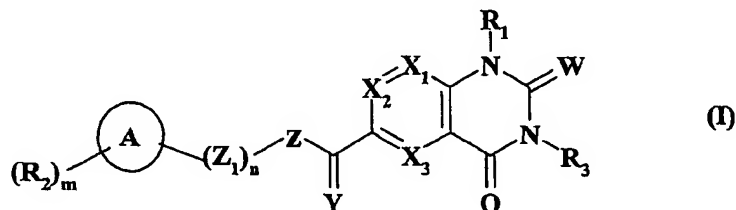
**Scheme 5 / Method B**

in which  $\text{R}_3$  is as defined for the compound of general formula (I).

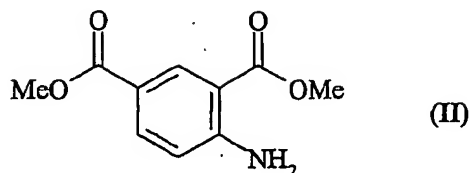
According to yet another aspect, an intermediate compound of general formula (III), in which  $\text{R}_3$  is a benzyl radical, may be obtained, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method C illustrated in Synthetic Scheme 6 below:

**Scheme 6 / Method C**

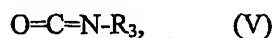
Consequently, a subject of the invention is also a process for manufacturing a compound of general formula (I):



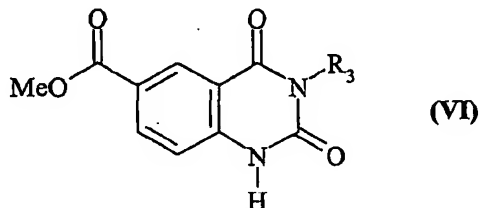
the said process being characterized in that it comprises the reaction of a compound of formula (II):



with pyridine and the compound of general formula (V):

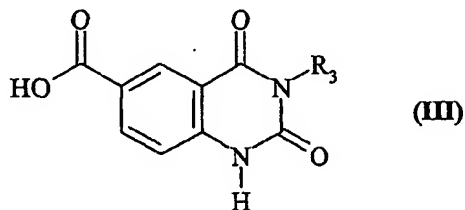


in which  $\text{R}_3$  is as defined in the summary of the invention, to give the compound of general formula (VI):

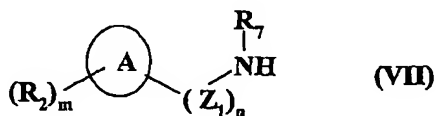


in which  $\text{R}_3$  is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which  $\text{R}_3$  is as defined in the summary of the invention.



The above process is also characterized in that the compound of general formula (III) in which  $\text{R}_3$  is as defined for the compound of general formula (I), is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII):

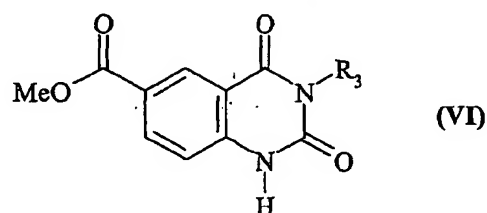


in which  $\text{R}_7$  is selected from hydrogen,  $(\text{C}_1-\text{C}_6)$ alkyl, aryl $(\text{C}_1-\text{C}_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A,  $\text{R}_2$ ,  $\text{Z}_1$ , m and n are as defined for the compound of general formula (I),

to give the compound of general formula (I) in which  $R_1$  represents H,  $X_1$ ,  $X_2$  and  $X_3$  are CH, Y is O, Z is N- $R_7$ , W is O, and A,  $R_2$ ,  $R_3$ ,  $Z_1$ , m and n are as defined hereinbefore.

The present invention also relates to a process for manufacturing a compound of general formula (I) in which  $R_1$ ,  $R_2$ ,  $R_3$ , A,  $Z_1$ , m and n are as defined for the compound of general formula (I),  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O and Z is N- $R_7$ ,

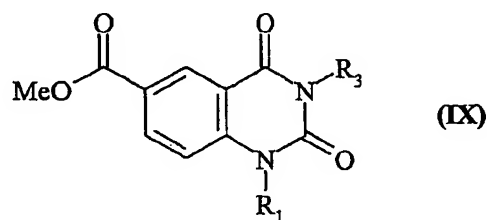
the said process being characterized in that a compound of general formula (VI):



in which  $R_3$  is as defined in the summary of the invention,

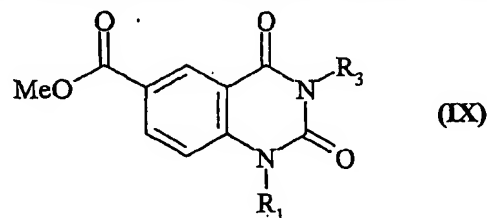
is reacted, in the presence of a base, with compound (VIII) of general formula X- $R_1$ , in

which  $R_1$  is as defined in the summary of the invention and  $X$  is a leaving group such as halogen, to give the compound of general formula (IX):



in which  $R_1$  and  $R_3$  are as defined hereinbefore.

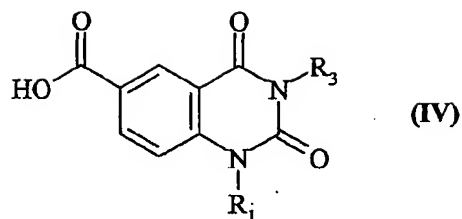
The above process is also characterized in that the compound of general formula (IX):



is reacted in the presence of LiOH to give the compound of general formula (IV):

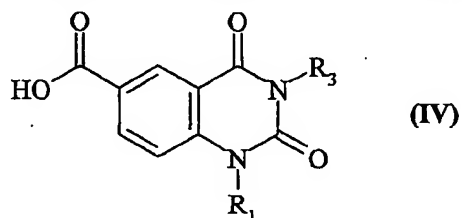


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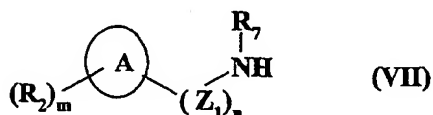


in which  $R_1$  and  $R_3$  are as defined hereinbefore.

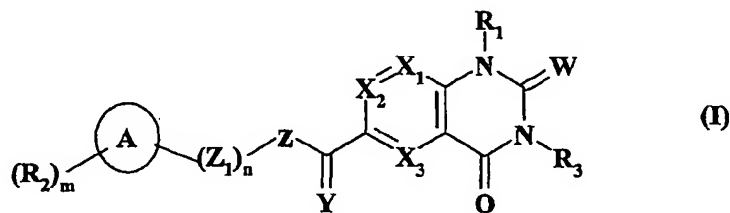
The above process is also characterized in that the compound of general formula (IV):



- 5 in which  $R_3$  is as defined in the compound of general formula (I),  
is reacted, in the presence of an acid activator such as TOFU, with the compound of  
general formula (VII)



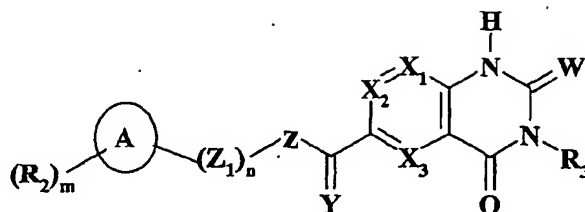
- 10 in which  $R_7$  is selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl and  
heteroaryl, and A,  $R_2$ ,  $Z_1$ , m and n are as defined in the summary of the invention, to give  
the compound of general formula (I):



in which  $R_1$ ,  $R_2$ ,  $R_3$ , A,  $Z_1$ , m and n are as defined in the summary of the invention,  $X_1$ ,  $X_2$   
and  $X_3$  are CH, W is O, Y is O and Z is N- $R_7$ .

- 15 Another subject of the present invention is a process for manufacturing the compound of  
general formula (I) in which  $R_1$ ,  $R_2$ ,  $R_3$ , W,  $X_1$ ,  $X_2$ ,  $X_3$ , A,  $Z_1$ , m and n are as defined for

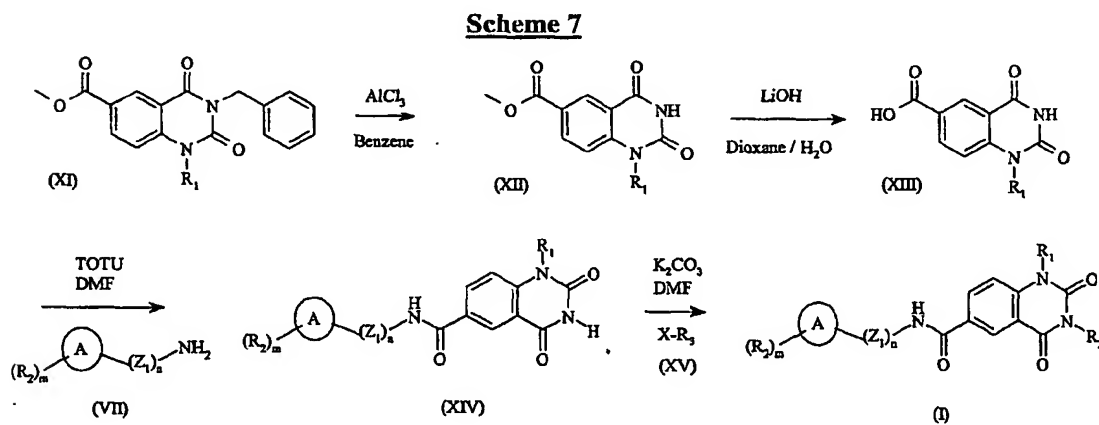
the compound of general formula (I), Y is O and Z is N-R<sub>7</sub>, characterized in that a compound of general formula (I) in which R<sub>1</sub> is H,



is reacted, in the presence of a base, with a compound (VIII) of general formula X-R<sub>1</sub>, in which R<sub>1</sub> is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which R<sub>1</sub> is as defined in the summary of the invention.

### C. Synthetic process No. 2

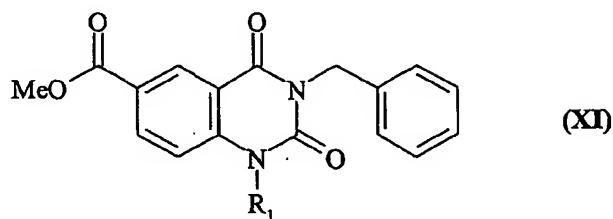
The compounds of the present invention can also be obtained by the method represented in Scheme 7 below:



in which each of the generic substituents is as defined for the compound of general formula (I).

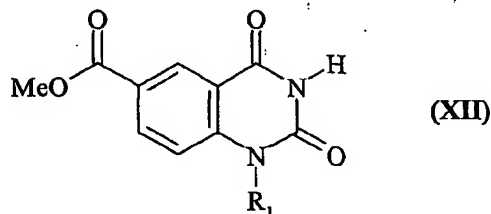
The present invention also relates to a process for manufacturing a compound of general formula (I) in which X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, W is O, Y is O, Z is N-R<sub>7</sub>, R<sub>1</sub>, R<sub>3</sub>, A, R<sub>2</sub>, Z<sub>1</sub>, m

and n are as defined for the compound of general formula (I) characterized in that a compound of general formula (XI):



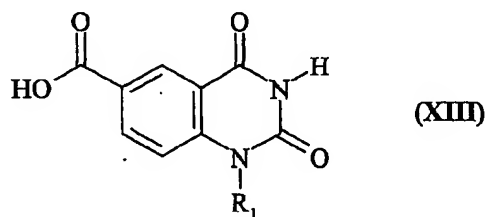
in which R<sub>1</sub> is as defined hereinbefore,

- 5     is reacted with AlCl<sub>3</sub> in a solvent such as benzene, to give the compound of general formula (XII):



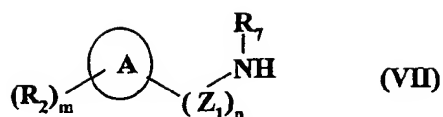
in which R<sub>1</sub> is as defined hereinbefore.

- 10     The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XII) is reacted in the presence of LiOH and a mixture of dioxane/H<sub>2</sub>O to give the compound of general formula (XIII):



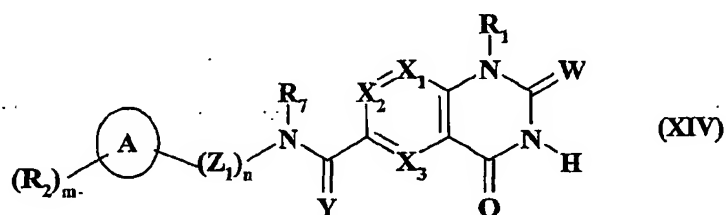
in which R<sub>1</sub> is as defined hereinbefore.

- 15     The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIII) is reacted, in the presence of an acid activator such as TOTU with the compound of general formula (VII):



in which R<sub>7</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A, R<sub>2</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention.

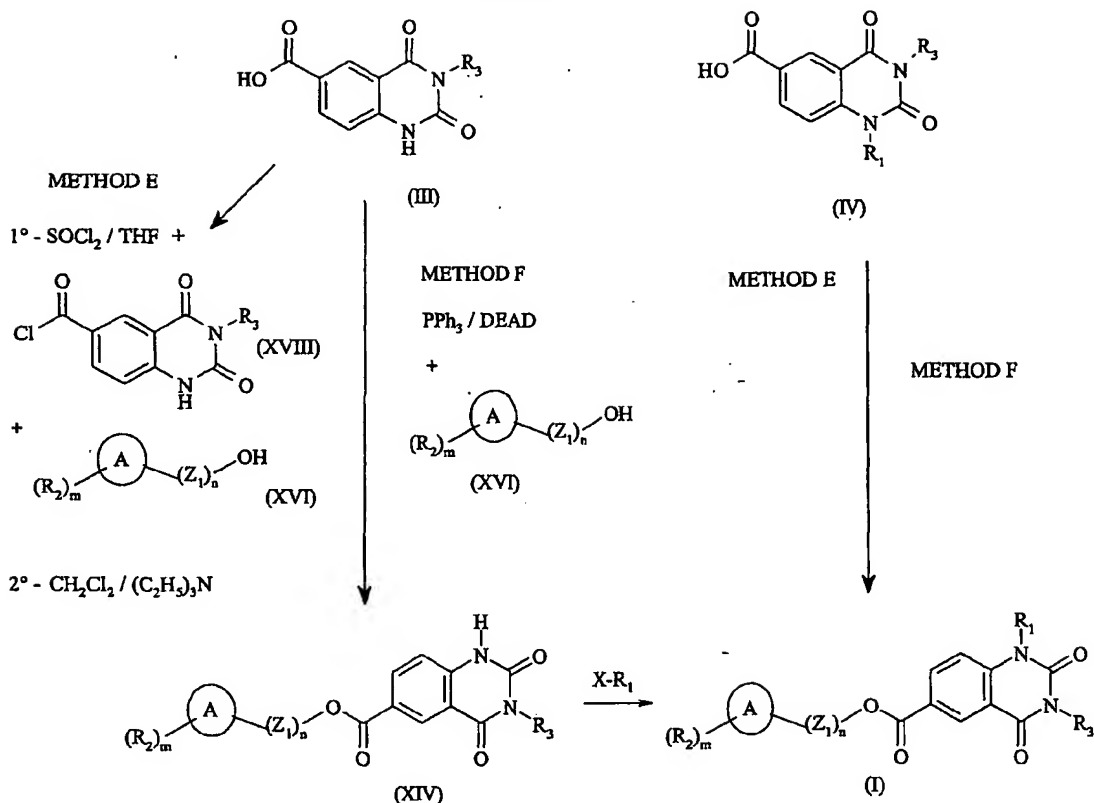
to give the compound of general formula (XIV) in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O, and  $R_7$ ,  $R_1$ , A,  $R_2$ ,  $Z_1$ , m and n are as defined hereinbefore:



The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIV) is reacted with compound (XV) of general formula  $X-R_3$ , in which  $R_3$  is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O, Z is  $N-R_7$ , and  $R_7$ ,  $R_1$ , A,  $R_2$ ,  $Z_1$ , m and n are as in the compound of general formula (I).

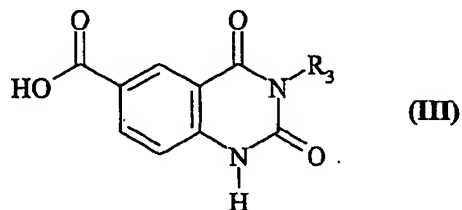
### **D. Preparation process No. 3**

The compounds of general formula (I) of the present invention may also be obtained by the method represented in Scheme 8 below:

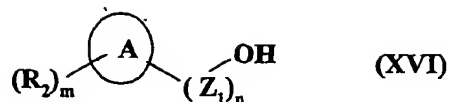
**Scheme 8**

In this scheme, each generic substituent is as defined for the compound of general formula (I) above.

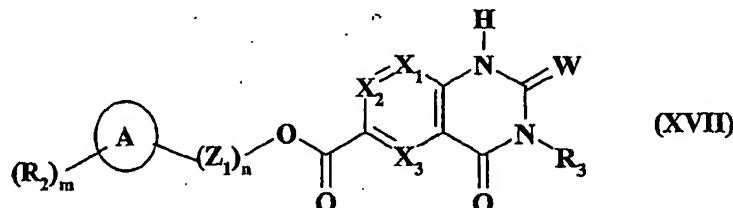
Thus, the present invention also relates to a process for manufacturing a compound of general formula (I) as defined above in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O and Z is O, characterized in that a compound of general formula (III):



in which  $R_3$  is as defined in the compound of general formula (I), is reacted with a compound of general formula (XVI):



in which A, R<sub>2</sub>, Z<sub>1</sub>, m and n are as defined in the compound of general formula (I), to give a compound of general formula (XVII):



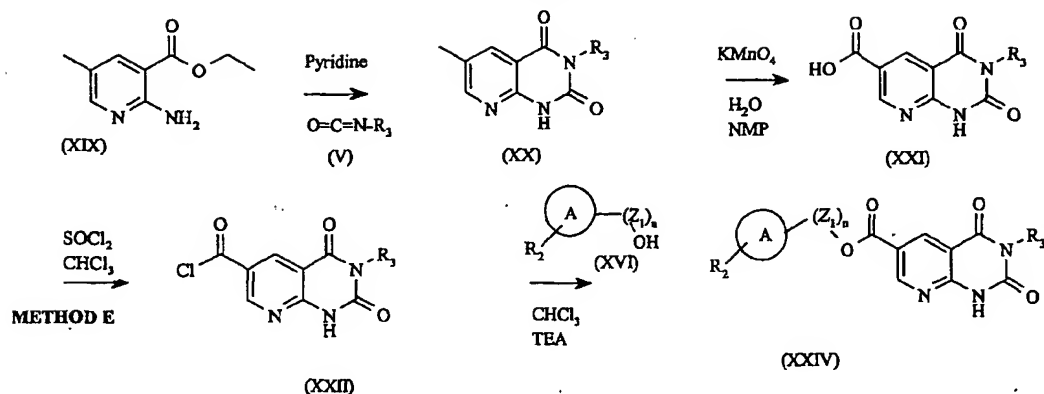
- 5 in which A, R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, and W is O.

According to the process for manufacturing a compound of general formula (I) above, the said process also comprises a step in which the compound of formula (XVII) is reacted, in the presence of a base, with compound (VIII) of general formula X-R<sub>1</sub>, in which R<sub>1</sub> is as  
 10 defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, W is O, Y is O, Z is O, and A, R<sub>2</sub>, R<sub>3</sub>, R<sub>1</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention

The present invention also relates to a process for manufacturing a compound of general formula (I) as defined above, characterized in that it comprises a step in which a compound  
 15 of general formula (IV) is reacted with a compound of general formula (XVI) to give a compound of general formula (I) in which X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, W is O, Y is O and Z is O.

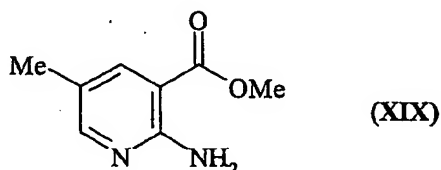
#### E. Preparation process No. 4

The compounds of the present invention, and most particularly the compounds of the  
 20 invention which constitute pyridine esters, may be obtained by the method represented in Scheme 9 below:

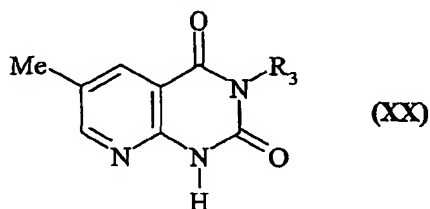
**Scheme 9**

in which each of the generic substituents on the intermediate compounds has the same  
 5 meaning as for the compound of general formula (I) as defined in the summary of the invention.

Consequently, a subject of the present invention is also a process for manufacturing a  
 compound of general formula (I) in which  $X_2$  and  $X_3$  are  $CH$ ,  $X_1$  is  $N$ ,  $Z$  is  $O$  and  $Y$  is  $O$ ,  
 10 characterized in that the said process comprises a step in which a compound of general formula (XIX):



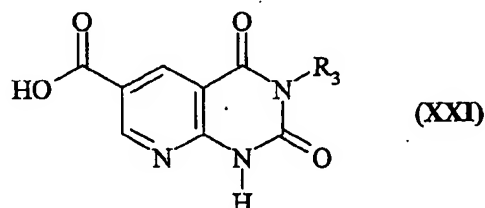
is reacted with pyridine and a compound (V) of general formula  $O=C=N-R_3$  in which  $R_3$  is  
 as defined in the compound of general formula (I),  
 to give a compound of general formula (XX):



15

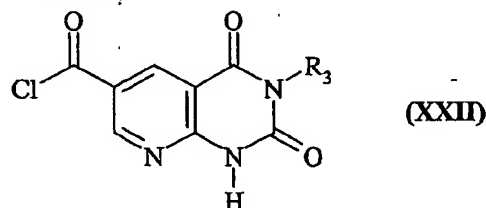
in which  $R_3$  is as defined hereinbefore.

The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XX) is reacted in the presence of  $\text{KMnO}_4$  to give the compound of general formula (XXI):



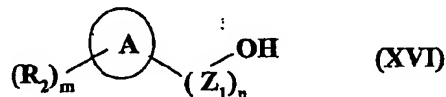
5 in which  $R_3$  is as defined hereinbefore.

The above process is also characterized in that it comprises a step in which a compound of general formula (XXI) is reacted in the presence of  $\text{SOCl}_2$  and  $\text{CHCl}_3$  to give the compound of general formula (XXII):



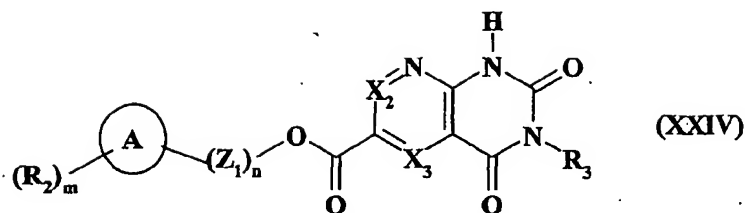
10 in which  $R_3$  is as defined hereinbefore.

The process for manufacturing a compound of general formula (I) according to the invention is also characterized in that it comprises a step in which the compound of formula (XXII) is reacted with the compound of general formula (XVI):



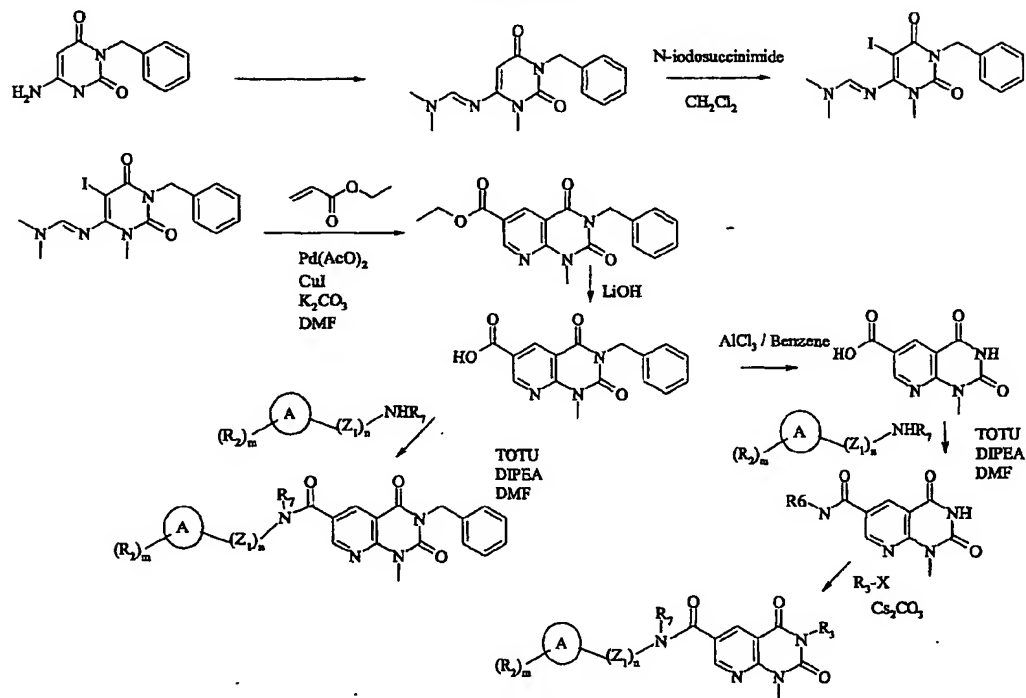
15 in which A,  $R_2$ ,  $Z_1$ , m and n are as defined in the compound of general formula (I), to give the compound of general formula (XXIV) in which  $X_2$  and  $X_3$  are CH and A, n, m,  $Z_1$ ,  $R_2$  and  $R_3$  are as defined in the summary of the invention/



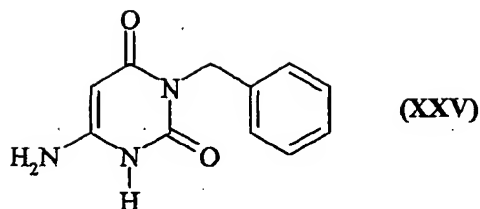


The compounds of the present invention which constitute pyridine amide can also be obtained by the method represented in scheme 10 below:

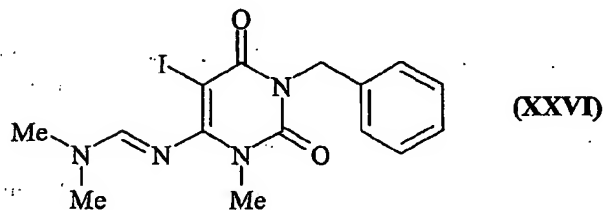
**Scheme 10**



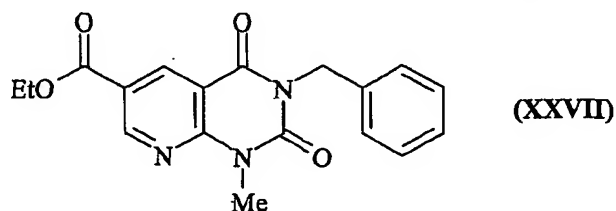
Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which  $X_2$  and  $X_3$  are  $CH$ ,  $X_1$  is  $N$ ,  $Z$  is  $-NR_7$  in which  $R_7$  is as defined in the compound of formula (I),  $W$  is  $O$ , and  $Y$  is  $O$ , characterized in that the said process comprises a step in which a compound of general (XXV):



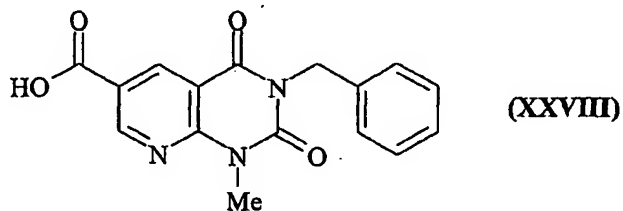
is reacted in a first step with *N,N'*-dimethylformamide dimethyl acetal under reflux of DMF, and in a second step with *N*-iodosuccinimide, to give a compound of formula (XXVI):



followed by reacting the compound of formula (XXVI) with ethyl acrylate in the presence of palladium diacetate, CuI and a base, to give the compound of general formula (XXVII):

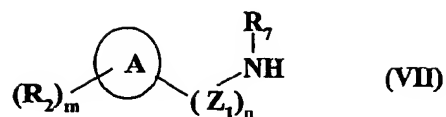


followed by reacting the compound of formula (XXVII) in the presence of LiOH to give the compound of general formula (XXVIII):

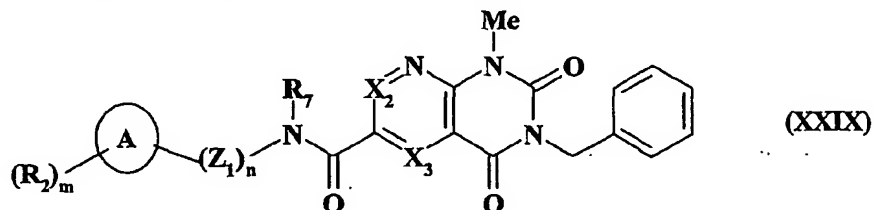


the said compound of formula (XXVIII):

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):



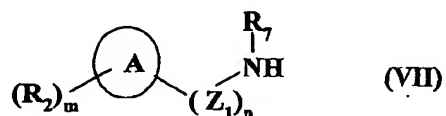
in which  $\text{R}_7$  is selected from hydrogen,  $(\text{C}_1\text{-C}_6)$ alkyl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{Z}_1$ ,  $m$  and  $n$  are as defined in the summary of the invention, to give the compound of general formula (XXIX):



5

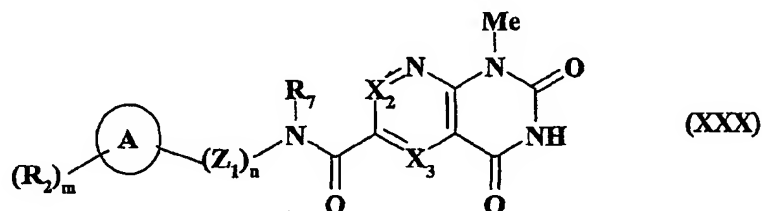
in which  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_7$ ,  $\text{Z}_1$ ,  $m$  and  $n$  are as defined hereinbefore, and  $\text{X}_2$  and  $\text{X}_3$  represents each  $-\text{CH}$  group,

- or is reacted in a first step with  $\text{AlCl}_3$  in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):



10

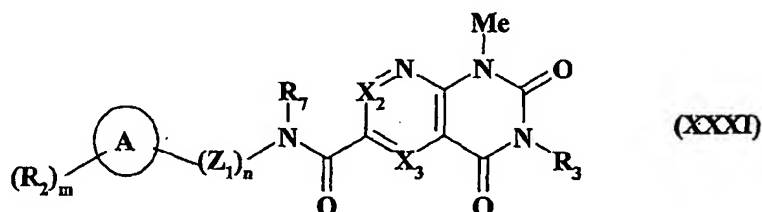
in which  $\text{R}_7$  is selected from hydrogen,  $(\text{C}_1\text{-C}_6)$ alkyl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and  $\text{A}$ ,  $\text{R}_2$ ,  $\text{Z}_1$ ,  $m$  and  $n$  are as defined in the summary of the invention, to give the compound of general formula (XXX):



15

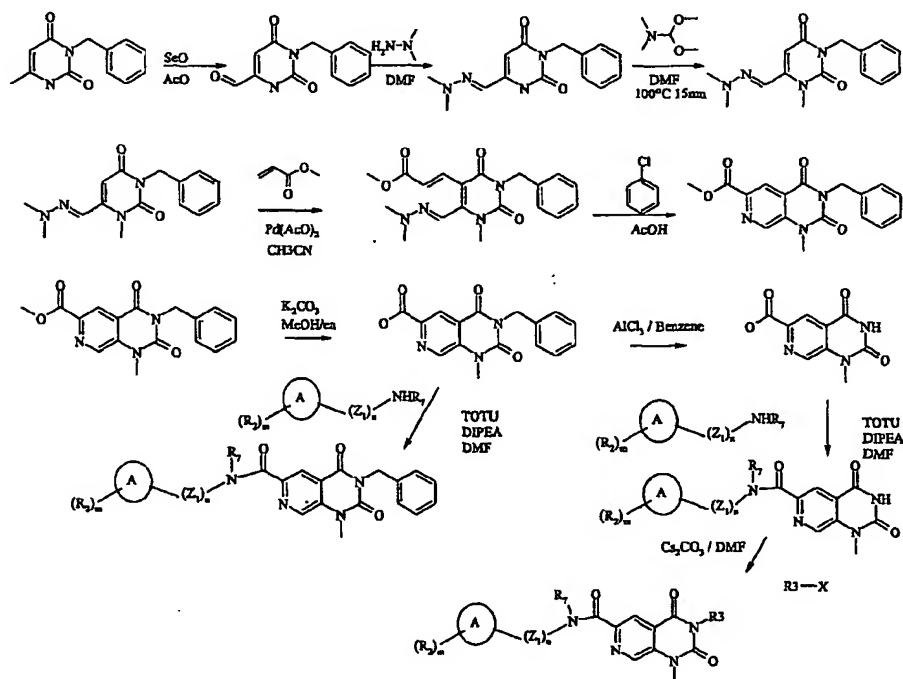
in which  $\text{A}$ ,  $\text{R}_2$ ,  $\text{R}_7$ ,  $\text{Z}_1$ ,  $m$  and  $n$  are as defined hereinbefore, and  $\text{X}_2$  and  $\text{X}_3$  represents each  $-\text{CH}$  group,

followed by reacting the compound of formula (XXX) with a compound of formula  $R_3-X$  in which  $R_3$  is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXI):



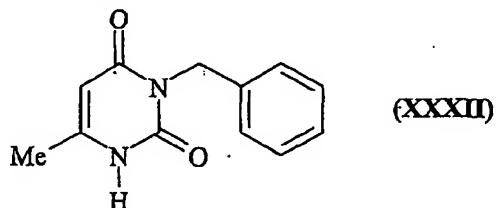
- 5 The compounds of the present invention which constitute pyridine amide, and particularly pyrido[3,4-d]pyrimidine derivatives, can also be obtained by the method represented in scheme 11 below:

**Scheme 11**

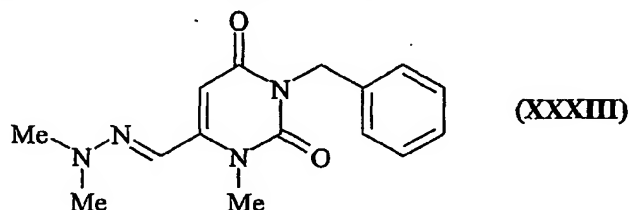


- 10 Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which  $X_1$  and  $X_3$  are CH,  $X_2$  is N, Z is  $-NR_7$  in which

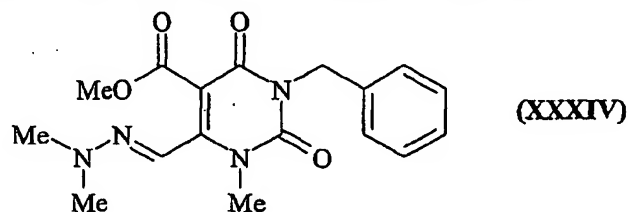
R<sub>7</sub> is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXXII):



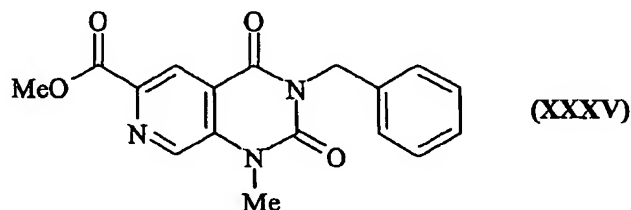
is reacted in a first step with selenium dioxide in the presence of acetic acid, in a second step with dimethylhydrazine, and in a third step with N,N'-dimethylformamide dimethylacetal under reflux of DMF, to give a compound of formula (XXXIII):



followed by reacting the compound of formula (XXXIII) with methyl acrylate in the presence of palladium diacetate, to give the compound of general formula (XXXIV):

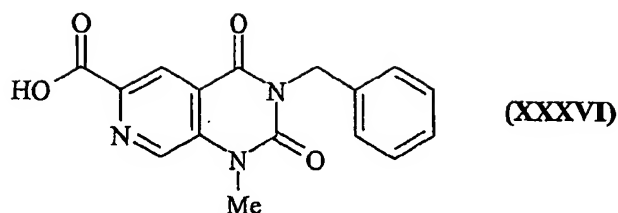


followed by reacting the compound of formula (XXXIV) with chlorobenzene and acetic acid to give the compound of formula (XXXV):



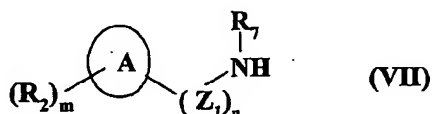
followed by reacting the compound of formula (XXXV) in the presence of a base to give the compound of general formula (XXXVI):

56



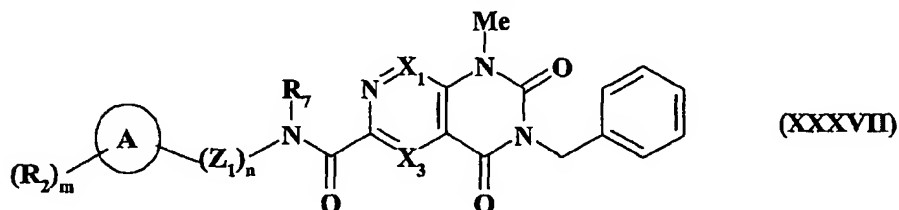
the said compound of formula (XXXVI) :

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):



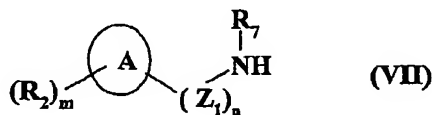
5

in which  $R_7$  is selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A,  $R_2$ ,  $Z_1$ , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVII):

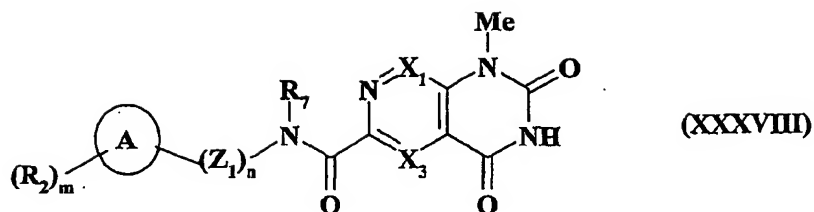


10 in which A,  $R_2$ ,  $R_7$ ,  $Z_1$ , m and n are as defined hereinbefore, and  $X_1$  and  $X_3$  represents each -CH group,

- or is reacted in a first step with  $AlCl_3$  in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):

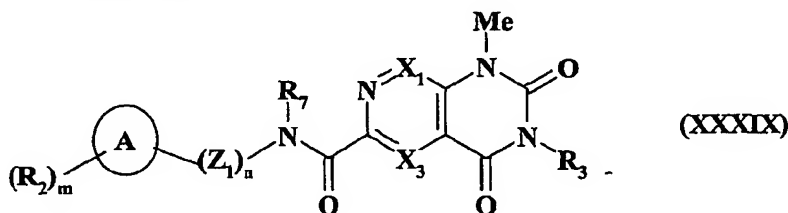


15 in which  $R_7$  is selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A,  $R_2$ ,  $Z_1$ , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVIII):



in which A, R<sub>2</sub>, R<sub>7</sub>, Z<sub>1</sub>, m and n are as defined hereinbefore, and X<sub>1</sub> and X<sub>3</sub> represents each -CH group,

5 followed by reacting the compound of formula (XXXVIII) with a compound of formula R<sub>3</sub>-X in which R<sub>3</sub> is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXIX):



The present invention is also illustrated, without being limited thereby, in the examples which follow.

## 10 EXAMPLES:

### Preparation A : Dimethyl 4-aminoisophthalate

#### Preparation according to Scheme 2:

##### **Step 1-2 : 4-Nitroisophthalic acid**

25 g (138 mmol) of 5-methyl-2-nitrobenzoic acid are suspended in 300 ml of water. 5 g  
 15 (89.1 mmol) of KOH are added for dissolution. The medium is heated to 90°C and 158 g of KMnO<sub>4</sub> (414 mmol) are added portionwise, rinsing with H<sub>2</sub>O. After 3 hours, the reaction medium is filtered through Celite and the filtrate is acidified to pH 1 with concentrated HCl. The precipitate obtained is filtered off and dried under vacuum.

**Weight = 15.3 g ; Yield = 53%**

**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm) 5.62-5.70 (d,1H); 7.88 (d,1H); 8.16 (s,1H)

**Step 2-2 : Dimethyl 4-nitroisophthalate**

12.75 g (60.4 mmol) of 4-nitroisophthalic acid from the above stage and 13 ml of  $\text{H}_2\text{SO}_4$  and 100 ml of methanol are maintained at reflux overnight. After cooling, the methanol is removed under vacuum. The residue is dissolved in 400 ml of EtOAc. The organic phase is washed with 50 ml of  $\text{H}_2\text{O}$  and then with 50 ml of 5%  $\text{NaHCO}_3$  solution.

Drying over  $\text{MgSO}_4$  and concentration under vacuum gives a crystalline residue.

**Weight = 12.17 g      Yield = 84%**

**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm) 3.86 (s,3H); 3.91 (s,3H); 8.16 (d,1H); 8.29-8.34 (m,2H)

**Step 3-2: Dimethyl 4-aminoisophthalate**

The compound from the above stage is reduced with hydrogen in the presence of palladium as catalyst.

Filtration through Celite and concentration gives:

**Weight = 5.12 g    Yield = 70%**

**m.p. = 127-128°C**

**NMR:**  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm) 3.87 (s,3H); 3.88 (s,3H); 6.30 (brs,2H); 6.65 (d,1H); 7.89 (dd,1H); 8.57 (d,1H)

**Preparation according to Scheme 3 - J. Org. Chem., 1997, 62 (12), 4088-4096**

**Step 1-3: Dimethyl 4-amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylate**

526 ml of benzene and 250 ml of methyl acrylate are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under inert atmosphere and protected from moisture, followed by 10 g (70.8 mmol) of methyl 5-amino-2-furan carboxylate. The mixture is brought to reflux and maintained for 24 hours. The reaction medium is concentrated to dryness on a rotavapor at  $50^\circ\text{C}$  under a vacuum of 20 mm Hg. The residue obtained is purified by flash chromatography using dichloromethane progressively enriched with ethyl acetate as solvent. The product is obtained as follows:

**Weight = 15 g of a yellow precipitate    Yield = 93%**



TLC: CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 70/30 v/v R<sub>f</sub> = 0.35

m.p. = 101.3°C

NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm) 2.87 (d,1H); 2.93 (d,1H); 3.20 (s,1H); 3.71 (s,3H); 3.82 (s,3H); 6.02 (d,1H); 5.60-6.40 (brs,2H); 6.17 (d,1H)

5           **Step 2-3 : Dimethyl 4-aminoisophthalate**

15 g (66 mmol) of compound obtained in Step 1-3 and 600 ml of benzene are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under an inert atmosphere and protected from moisture. 13.8 g (12 ml, 98 mmol) of BF<sub>3</sub> etherate are added with stirring. The mixture is refluxed for 2 minutes and then cooled to room  
10 temperature and, after addition of saturated NaHCO<sub>3</sub> solution (pH 9), the phases are separated by settling. The aqueous phase is re-extracted twice with dichloromethane. The organic phases are combined and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvents under vacuum, the 13.8 g of residue are purified by chromatography using dichloromethane as elution solvent. The product is obtained as follows:

15   **Weight = 8.5 g of a crystalline residue   Yield = 62%**

TLC: CH<sub>2</sub>Cl<sub>2</sub>. R<sub>f</sub> = 0.30

m.p. = 130.1°C

NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm) 3.87 (s,3H); 3.88 (s,3H); 6.30 (brs,2H); 6.65 (d,1H); 7.89 (dd,1H); 8.57 (d,1H)

20   **Preparation B : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

**Preparation according to Scheme 4:**

**Step 1-4 : Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
-6-carboxylate**

4 g (19.1 mmol) of compound of preparation A and 40 ml of pyridine are successively  
25 introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture, followed by addition of 3.2 g (24 mmol) of benzyl isocyanate. The colourless solution is stirred and heated at 95-100°C. After 6 hours at this temperature, 1 ml of benzyl isocyanate is added and stirring is then continued at 100°C overnight. The

next day, the reaction medium is cooled and poured into 400 ml of a water + ice mixture, it is left stirring for about 30 minutes and the precipitate obtained is then filtered off. The product is re-slurried at reflux in 150 ml of ethanol. After cooling, the product is filtered off. The product is obtained as follows:

5     **Weight = 3.7 g     Yield = 62%**

**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.75 (s,3H); 4.95 (s,2H); 7.1-7.2 (m,6H); 8.05 (d,1H); 8.35 (s,1H); 11.8 (bs,1H)

**Step 2-4 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

1.5 g (4.84 mmol) of methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate, 14 ml of dioxane and 48 ml of  $\text{H}_2\text{O}$  are introduced into a 100 ml round-bottomed flask fitted with a reflux condenser. 0.41 g (9.68 mmol) of hydrated lithium hydroxide is added to the suspension with stirring. The mixture is brought to reflux and maintained for about 1 hour (solution). After cooling in an ice bath, the medium is acidified to pH 1 with concentrated hydrochloric acid. The very-fine precipitate obtained is filtered off, to give:

15     **Weight: 1.3 g     Yield = 96%**

**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 5.1 (s,2H); 7.2-7.35 (m,6H); 8.15 (d,1H); 8.48 (s,1H); 11.85 (s,1H); 13.1 (bs,1H)

**Preparation according to Scheme 5:**

20     **Step 1-5 : Dimethyl 4-(3-benzylureido)isophthalate**

10 g (48 mmol) of compound of Preparation A, 200 ml of anhydrous toluene, about 100 mg of animal charcoal and then 12 g (40 mmol) of triphosgene are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The suspension is stirred and maintained at the reflux point of the toluene for 2 hours. The reaction medium is filtered through infusorial earth and then concentrated to dryness at 50°C under a vacuum of about 20 mm Hg. The residue obtained is dissolved in 200 ml of anhydrous toluene and stirred.

4.7 ml (43 mmol) of benzylamine are added to this solution over a few minutes. A precipitate is immediately formed. 200 ml of toluene are added to facilitate stirring, and the mixture is maintained at room temperature overnight. The next day, the precipitate is

filtered off and washed successively with toluene and ether. After drying under vacuum, the product is obtained as follows:

**Weight** 13.9 g    **Yield** = 84.6%

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/acetone 98/2 R<sub>f</sub> = 0.35

5    **m.p.** = 181.9°C

**NMR:** DMSO <sup>1</sup>H δ (ppm) 3.8 (s,3H); 3.9 (s,3H); 4.3 (s,2H); 7.2-7.4 (m,5H); 8.0 (d,1H); 8.3 (s,1H); 8.5 (s,1H); 8.55 (d,1H); 10.2 (s,1H)

**Step 2-5 : Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
-6-carboxylate**

10    13.7 g (40 mmol) of compound obtained in Step 1-5, 300 ml of methanol and then 1.3 g (24 mmol) of sodium methoxide are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The white suspension is maintained at reflux for 3 hours (the suspension changes form). Half of the methanol is removed on a rotavapor at 50°C under vacuum. The mixture is cooled and acidified to pH 4 with 2 ml of  
15    concentrated hydrochloric acid. It is left stirring for 15 minutes while cold and the crystalline residue obtained is then filtered off.

**Weight** = 12 g    **Yield** = 96.7%

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/acetone 98/2

**R<sub>f</sub>** = 0.05-0.2

20    **m.p.** = 248.1°C

**NMR:** DMSO <sup>1</sup>H δ (ppm) 3.9 (s,3H); 5.1 (s,2H); 7.2-7.4 (m,6H); 8.15 (d,1H); 8.45 (s,1H); 11.9 (bs,1H)

**Step 3-5 : 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The product is obtained according to the procedure of Step 2-4 of Preparation B using the  
25    compound obtained in preceding Step 2-5.

**Preparation according to Scheme 6:**

**Step 1-6 : 3-Benzyl-6-bromo-1H-quinazoline-2,4-dione**

10 g (46.3 mmol) of 2-amino-5-bromobenzoic acid, 100 ml of anhydrous pyridine and 6.16 g (46.3 mmol) of benzyl isocyanate are introduced into a 250 ml one-necked flask

fitted with a reflux condenser and protected from moisture. The solution is maintained at reflux with stirring for 36 hours. The reaction mixture is cooled and H<sub>2</sub>O is added until the start of precipitation. The mixture is left to crystallize for about 1 hour and the precipitate obtained is then filtered off and washed. The 8 g of crude product are purified by reslurrying in refluxing ethanol.

**Weight:** 3.4 g

**NMR:** = DMSO <sup>1</sup>H δ (ppm): 4.9 (s,2H); 7.0 (d,1H); 7.03-7.2 (m,5H); 7.65 (d,1H); 7.85 (s,1H); 11.5 (s,1H)

**Step 2-6 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carbonitrile**

2.5 g (7.5 mmol) of compound of Step 1-6, 1.215 g (13.6 mmol) of copper cyanide and 22.5 ml of 1-methyl-2-pyrrolidinone are introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture. The beige-coloured solution obtained is refluxed at an internal temperature of 200°C for 1 h 30 min.

The reaction medium is concentrated to dryness at 80°C under a vacuum < 1 mm Hg. The residue is taken up in 300 ml of 2N NH<sub>4</sub>OH and extracted 3 times with dichloromethane. The presence of an insoluble material is noted, this material being taken up twice in 20 ml of a 50/50 v/v MeOH/CH<sub>2</sub>Cl<sub>2</sub> mixture. The organic phases are combined and washed with H<sub>2</sub>O. After drying over Na<sub>2</sub>SO<sub>4</sub> and concentration under vacuum, the black residue obtained is crystallized from 10 ml of CH<sub>2</sub>Cl<sub>2</sub>. The product is obtained as follows:

**Weight:** 1.2 g      **Yield** = 60%

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10      R<sub>f</sub> = 0.50

**NMR:** DMSO <sup>1</sup>H δ (ppm): 4.82 (s,2H); 6.97-7.12 (m,6H); 7.80 (d,1h); 8.1 (s,1H); 11.75 (bs,1H)

**Step 3-6 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

1.4 g (5.05 mmol) of compound of Step 2-6 and 35 ml of H<sub>2</sub>O are introduced into a 100 ml one-necked flask fitted with a reflux condenser, followed by cautious addition of 35 ml of H<sub>2</sub>SO<sub>4</sub>. The suspension is maintained at reflux with stirring for 3 hours. After cooling, the beige-coloured precipitate is filtered off and washed to neutrality with H<sub>2</sub>O and then with methanol.

**Weight:** 1.5 g      **Yield** = 100%

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.10

m.p. = 360°C

**Preparation C : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline**  
**-6-carboxylic acid**

5           **Step 1: Methyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline**  
              **-6-carboxylate**

11.8 g (38.0 mmol) of Preparation B, 120 ml of dimethylformamide and 7.9 g (57 mmol) of K<sub>2</sub>CO<sub>3</sub> are introduced into a 250 ml three-necked flask. The suspension is stirred for 15 minutes at room temperature. 27 g (12 ml, 190 mmol) of iodomethane are added over 2  
10 minutes. The suspension is stirred at room temperature for 30 to 45 minutes. The solvent is removed under vacuum and the residue is taken up in 500 ml of dichloromethane and washed with 3 times 300 ml of water. The organic phase is dried and the solvent is removed. The product is obtained as follows:

**Weight: 12 g           Yield = 97.4%**

15       **TLC: CH<sub>2</sub>Cl<sub>2</sub>/acetone 98/2 R<sub>f</sub> = 0.60**

**m.p. = 179.3°C**

**NMR: DMSO <sup>1</sup>H δ (ppm) 3.6 (s,3H); 3.90 (s,3H); 5.1 (s,2H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H)**

20           **Step 2: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic**  
              **acid**

The product is obtained with a yield of 100% (10 g) according to the procedure of Step 2-4 of Preparation B using 9.5 g (29.3 mmol) of compound obtained in Step 1.

**TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.50**

**m.p. = 227.2°C**

25       **NMR: DMSO <sup>1</sup>H δ (ppm) 3.55 (s,3H); 5.15 (s,2H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 13.2 (bs,1H)**

**Preparation D: 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-**  
**6-carboxylic acid**

**Step 1: Methyl 3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

5.5 g (26.3 mmol) of compound of the Preparation A and 50 ml of pyridine are introduced into a round-bottomed flask. 5.0g (33.1 mmol) of 3-fluorobenzyl isocyanate are added.

5 The mixture is maintained at reflux for 6 hours and 0.8 g (5.3 mmol) of 3-fluorobenzyl isocyanate is added in one portion. The mixture is heated overnight at reflux. The mixture is cooled and the product is precipitated with the addition of water and filtered. The product is reslurried in hot ethanol and filtered to provide 6.7 g (yield:78%) of the desired compound.

10 MS: m/z (APCI, AP+) 329.1 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 62.20; H, 3.99; N, 8.53.

Found (%) : C, 62.09; H, 3.85; N, 8.42.

**Step 2: Methyl 1-methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

15 1.8 g (5.5 mmol) of the product from the preceding Step 1 is dissolved in 30 ml of dimethylformamide and 1.8 g (8.1 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding iodomethane 1.1 g (8.1 mmol). Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated  
20 aqueous NaCl solution (4 x 20 ml), and dried MgSO<sub>4</sub>. Slurried solid product in hot ethyl acetate and filtered to obtain 1.7 g (yield : 90%) of the desired compound.

MS: m/z (APCI, AP+) 343.1 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 63.16; H, 4.42; N, 8.18.

Found (%) : C, 63.02; H, 4.26; N, 8.06.

25 **Step 3: 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

0.71 g of the compound (yield:76%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 329.0 [M]<sup>+</sup>

**CHN Analysis:** Calcd (%) : C, 62.20; H, 3.99; N, 8.53.

Found (%) : C, 61.94; H, 3.78; N, 8.57.

**Preparation E: 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

5

**Step 1: Methyl 1-ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

2.0 g (6.1 mmol) of the compound of Step 1 of Preparation D are dissolved in 30 ml of dimethylformamide and 1.96 g (9.2 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding 1.4 g (9.2 mmol) of iodoethane. Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO<sub>4</sub>. Slurried solid product in hot ethyl acetate and filtered to obtain 1.4 g (yield: 67%) of the desired compound.

15 **MS:** m/z (APCI, AP+) 357.1 [M]<sup>+</sup>

**CHN Analysis:** Calcd (%) : C, 64.04; H, 4.81; N, 7.86.

Found (%) : C, 63.72; H, 4.68; N, 7.75.

**Step 2: 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

20 1.1 g of the compound (yield: 71%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 1.

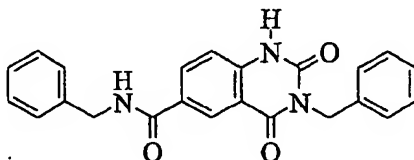
**MS:** m/z (APCI, AP+) 343.0 [M]<sup>+</sup>

**CHN Analysis:** Calcd (%) : C, 63.16; H, 4.42; N, 8.18.

Found (%) : C, 63.06; H, 4.41; N, 8.03.

25 Examples 1 to 461 illustrate, without limiting it, the synthesis of particularly active compounds of formula (I) according to the invention.

**Example 1: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide**



0.150 g (0.51 mmol) of compound of Preparation B and 8.0 ml of anhydrous  
5 dimethylformamide are introduced into a stirred 25 ml one-necked flask protected from  
moisture. 0.054 g (56  $\mu$ l, 0.51 mmol) of benzylamine and 0.17 g (0.51 mmol) of TOTU are  
added to this solution. The solution is cooled in a bath to 0°C. 0.132 g (0.18 ml,  
1.02 mmol) of N,N-diisopropylethylamine is then added. The mixture is warmed to room  
temperature and stirred overnight. After monitoring by TLC (90/10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH), the  
10 DMF is removed under vacuum. The crystalline residue obtained is taken up in  
dichloromethane with the amount of methanol required for total dissolution. The organic  
phase is washed successively with 40 ml of 1N HCl, 40 ml of H<sub>2</sub>O, 40 ml of saturated  
NaHCO<sub>3</sub> solution and finally 40 ml of H<sub>2</sub>O. The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and  
the solvents are removed under vacuum. 0.140 g of product is obtained, which is  
15 recrystallized from 30 ml of acetonitrile:

**Weight:** 0.110 g    **Yield** = 56%

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10    **R<sub>f</sub>** = 0.65

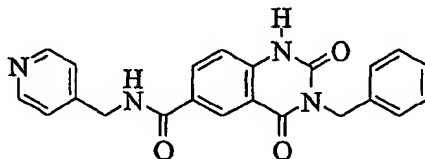
**NMR:** DMSO <sup>1</sup>H  $\delta$  (ppm): 4.45 (d,2H); 5.1 (s,2H); 7.1-7.4 (m,11H); 8.1 (d,1H); 8.5  
(s,1H); 9.15 (m,1H); 11.75 (bs,1H)

20 **IR:** 3425,2364,1722,1640,1509,1442,1304,1261,1078,927,845 cm<sup>-1</sup>

**m.p.** = 241.2°C

**HPLC:** 98.3%

**Example 2 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide**





The product is obtained with a yield of 46% (0.090 g) according to the procedure of Example 1 using 4-picolylamine, and after recrystallization from a 50/50 EtOAc/EtOH mixture.

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.60

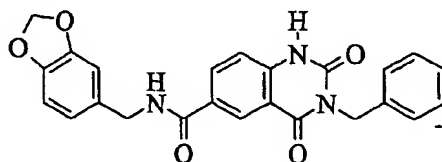
5 **NMR:** DMSO <sup>1</sup>H δ (ppm): 4.5 (d,2H); 5.1 (s,2H); 7.2-7.4 (m,8H); 8.15 (d,1H); 8.5 (d,2H); 8.55 (s,1H); 9.25 (t,1H); 11.75 (s,1H)

**IR:** 3250,1725,1669, 1642,1623,1450,1345,1301,1075,1006, 830 cm<sup>-1</sup>

**m.p.** = 305.2°C

**HPLC:** 95.1%

10 **Example 3 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**



The product is obtained with a yield of 64% (0.140 g) according to the procedure of Example 1 using piperonylamine, and after crystallization from acetonitrile.

15 **TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.65

**NMR:** DMSO <sup>1</sup>H δ (ppm): 4.35 (d,2H); 5.1 (s,2H); 5.95 (s,2H); 6.7-6.95 (m,3H); 7.15-7.4 (m,6H); 8.15 (d,1H); 8.5 (s,1H); 9.1 (t,1H); 11.7 (bs,1H)

**IR:** 3200,1727,1636, 1493,1444,1299,1261,1041,938,841,763,726 cm<sup>-1</sup>

**m.p.** = 256°C

20 **HPLC:** 99%

**Example 4: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-thienylmethyl)amide**

25 The product is obtained with a yield of 40% (0.080 g) according to the procedure of Example 1, but using 2-thienylmethylamine, and after a crystallization from acetonitrile.

**TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.65

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.35 (d,2H); 4.85 (s,2H); 6.7-6.85 (m,2H); 6.95-7.2 (m,7H); 7.9 (d,1H); 8.3 (s,1H); 9.05 (t,1H); 11.55 (bs,1H)

IR: 1729,1637,1511,1444,1346,1298,1261,1072,845,763  $\text{cm}^{-1}$

m.p. = 236.3°C

5 HPLC: 98.7%

**Example 5 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (3-pyridylmethyl)amide**

10 The product is obtained with a yield of 66% (0.130 g) according to the procedure of Example 1, but using 3-(aminomethyl)-pyridine, and after a crystallization from acetonitrile.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5  $R_f$  = 0.40

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.5 (d,2H); 5.15 (s,2H); 7.15-7.4 (m,7H); 7.7 (d,1H); 8.15 (d,1H); 8.45 (d,1H); 8.55 (d,2H); 9.25 (t,1H); 11.8 (s,1H)

15 IR: 3345,1716,1670,1638,1621,1450,1433,1348,1298,1068,829,774  $\text{cm}^{-1}$

m.p. = 252.3°C

HPLC: 97.4%

**Example 6: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide**

20

The product is obtained with a yield of 47.2% (0.100 g) according to the procedure of Example 1, but using 4-methoxybenzylamine, and after a crystallization from acetonitrile.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5  $R_f$  = 0.45

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.7 (s,3H); 4.4 (d,2H); 5.1 (s,2H); 6.9 (d,2H); 7.2-7.4 (m,8H); 8.15 (d,1H); 8.5 (s,1H); 9.15 (t,1H); 11.8 (bs,1H)

IR: 3400,3210,1727,1638,1513,1441,1300,1253,1173,1040,843, 760  $\text{cm}^{-1}$

m.p. = 269°C

HPLC: 100%

**Example 7: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-chlorobenzylamide**

- 5 The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-chlorobenzylamine, and after a crystallization from acetonitrile.  
TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.45  
NMR: DMSO <sup>1</sup>H δ (ppm): 4.5 (d,2H); 5.1 (s,2H); 7.2-7.45 (m,10 H); 8.15 (d,1H); 8.5 (s,1H); 9.25 (t,1H); 11.8 (bs,1H)  
10 IR: 3365,3200,1726,1638,1551,1512,1444,1305,1263,1012,844, 763 cm<sup>-1</sup>  
m.p. = 280.6°C  
HPLC: 98.1%

**Example 8: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methylbenzylamide**

- 15 The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-methylbenzylamine, and after a crystallization from acetonitrile.  
TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.40  
NMR: DMSO <sup>1</sup>H δ (ppm): 2.3 (s,3H); 4.4 (d,2H); 5.1 (s,2H); 7.0-7.4 (m,10H); 8.15 (d,1H); 8.55 (s,1H); 9.1 (t,1H); 11.8 (bs,1H)  
20 IR: 3280,1720,1671,1640,1623,1550,1278,848,774,744 cm<sup>-1</sup>  
m.p. = 267.8°C  
HPLC: 98.7

**Example 9: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

- 25 0.500 g (1.61 mmol) of compound of Preparation C in 25 ml of anhydrous dimethylformamide are introduced into a stirred 50 ml one-necked flask protected from moisture. 0.244 g (0.201 ml, 1.61 mmol) of piperonylamine and 0.531 g (1.61 mmol) of  
30 TOTU are added to this solution. The solution is cooled in a cold bath to 0°C. 0.415 g

(0.564 ml, 3.22 mmol) of N,N-diisopropylethylamine is then added. The mixture is warmed to room temperature and stirred overnight.

After monitoring by TLC (90/10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH), DMF is removed under vacuum. The crystalline residue obtained is taken up in dichloromethane. The organic phase is washed successively with 1N HCl, H<sub>2</sub>O, saturated NaHCO<sub>3</sub> and finally H<sub>2</sub>O. The organic phase is dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent is removed under vacuum. 0.540 g of product, recrystallized from 30 ml of acetonitrile, is obtained as follows:

Weight: 0.390 g Yield = 54.6%

TLC: CH<sub>2</sub>Cl<sub>2</sub>/acetone 90/10 R<sub>f</sub> = 0.40

10 NMR: DMSO-<sup>1</sup>H δ (ppm): 3.55 (s,3H); 4.35 (d,2H); 5.15 (s,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

IR: 3303,1703,1656,1637,1498,1444,1322,1254,1040,932,845 cm<sup>-1</sup>

m.p. = 215.1°C

HPLC: 99.5%

15 **Example 10: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide**

The product is obtained with a yield of 56.8% (0.110 g) according to the procedure of Example 9, but using benzylamine, and after a crystallization from acetonitrile.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/acetone 90/10 R<sub>f</sub> = 0.55

20 NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm) 3.65 (s,3H); 4.65 (d,2H); 5.3 (s,2H); 6.55 (m,1H); 7.2-7.6 (m,11H); 8.3 (d,1H); 8.5 (s,1H);

IR: 1708,1655,1641,1616,1507,1478,1326,1246,930,750 cm<sup>-1</sup>

m.p. = 198.9°C

HPLC: 100%

25 **Example 11: Methyl 4-({[1-(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)methanoyl]amino}methyl)benzoate**

The product is obtained with a yield of 61.5% (0.135 g) according to the procedure of Example 9, but using methyl 4-(aminomethyl)benzoate hydrochloride and 3.5 equivalents

of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient, followed by a solidification in ether.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.36

NMR: DMSO <sup>1</sup>H δ (ppm) : 3.55 (s,3H); 3.85 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2-7.35 (m,5H); 7.45 (d,2H); 7.6 (d,1H); 7.95 (d,2H); 8.3 (d,1H); 8.65 (s,1H); 9.35 (t,1H)

IR: 1723, 1706, 1657, 1642, 1617, 1506, 1477, 1284, 1109, 749 cm<sup>-1</sup>

m.p. = 196°C

HPLC: 100%

10 **Example 12: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide**

The product is obtained with a yield of 42% (0.090 g) according to the procedure of Example 9, but using 4-hydroxy-3-methoxybenzylamine hydrochloride and 3.5 equivalents of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient, followed by a solidification in ether.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.59

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.4 (d,2H); 5.15 (s,2H); 6.75 (s,2H); 6.95 (s,1H); 7.2-7.40 (m,6H); 7.55 (d,1H); 8.3 (d,1H); 8.65 (s,1H); 8.8 (s,1H); 9.15 (t,1H)

IR: 1707, 1655, 1618, 1502, 1477, 1277, 704 cm<sup>-1</sup>

20 m.p. = 183°C

HPLC: 87.1%

**Example 13: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide**

25 The product is obtained with a yield of 77.7% (0.320 g) according to the procedure of Example 9, but using 4-methoxybenzylamine. The crude product is purified by chromatography on silica, using 97/3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.8

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.2 (s,2H); 6.9 (d,2H); 7.2-7.4 (m,7H); 7.6 (d,1H); 8.3 (d,1H); 8.65 (s,1H); 9.25 (t,1H)

IR: 1705,1660,1636,1505,1251,750  $\text{cm}^{-1}$

m.p. = 191°C

5 HPLC: 97.3%

**Example 14: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide**

The product is obtained with a yield of 67.7% (0.130 g) according to the procedure of Example 9, but using 4-picolylamine.

The crude product is purified by chromatography on silica, using 95/5  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90/10  $R_f$  = 0.18

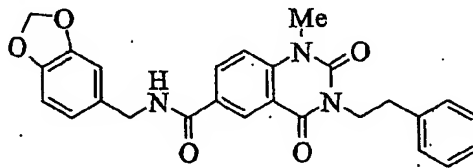
15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2-7.4 (m,7H); 7.6 (d,1H); 8.3 (d,1H); 8.5 (d,2H); 8.65 (s,1H); 9.35 (t,1H)

IR: 1705,1658,1634,1508,1332,831,749,705  $\text{cm}^{-1}$

m.p. = 172°C

HPLC: 98.8%

20 **Example 15: 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**



**Step 1: Methyl 2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

25 0.750 g (3.6 mmol) of compound of Preparation A and 7.5 ml of pyridine are introduced into a round-bottomed flask. 0.530 g (0.5 ml; 3.6 mmol) of phenethyl isocyanate is added.

The mixture is maintained at 100°C overnight. Since the reaction is incomplete, a second addition of phenethyl isocyanate, i.e. 2 equivalents, is carried out. After precipitation with H<sub>2</sub>O, filtration and purification by reslurrying in hot ethanol, the product is obtained as follows:

5     **Weight:** 0.640 g   **Yield** = 54.9%

**NMR:** DMSO <sup>1</sup>H δ (ppm): 2.85-2.95 (m, 2H); 4.90 (s, 3H); 4.05-4.15 (m, 2H); 7.15-7.3 (m, 6H); 8.15 (d, 1H); 8.45 (s, 1H); 11.8 (bs, 1H)

**Step 2: 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The product from the preceding step is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.500 g of the desired compound (yield : 80%).

10     **NMR:** DMSO <sup>1</sup>H δ (ppm) 2.85-2.95 (m, 2H); 4.05-4.15 (m, 2H); 7.15-7.3 (m, 6H); 8.15 (d, 1H); 8.45 (s, 1H); 11.75 (s, 1H); 13.05 (bs, 1H)

**Step 3: 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid  
(benzo[1,3]dioxol-5-ylmethyl)amide**

15     The product is obtained with a yield of 57.8% (0.205g) according to the procedure of Example 1, using 250 mg (0.8 mmol) of the compound obtained in the preceding Step 2 and piperonylamine.

**NMR:** DMSO <sup>1</sup>H δ (ppm): 2.9 (t, 2H); 4.1 (t, 2H); 4.4 (d, 2H); 5.95 (s, 2H); 6.75-6.95 (m, 3H); 7.15-7.35 (m, 6H); 8.1 (d, 1H); 8.5 (s, 1H); 9.1 (t, 1H); 11.65 (bs, 1H)

20     **IR:** 3249, 1704, 1658, 1636, 1488, 1251, 810, 753 cm<sup>-1</sup>

**m.p.** = 296°C

**HPLC:** 99.5%

**Step 4: 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-  
carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

25     0.190 g (0.46 mmol) of the product from the preceding Step 3, 2 ml of dimethylformamide and 0.095 g (0.68 mmol) of K<sub>2</sub>CO<sub>3</sub> are introduced into a 25 ml round-bottomed flask. The mixture is stirred for 15 min at room temperature and 0.325 g (0.15 ml, 2.29 mmol) of iodomethane is then added. Stirring is continued for 30 to 45 minutes. The solvent is

removed under vacuum. The residue is taken up in dichloromethane and washed with H<sub>2</sub>O. The organic phase is separated out after settling and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration under vacuum, the product is purified by chromatography on silica, using a 98/2 CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient, and then solidified in ether to provide 0.080g of the desired compound (yield : 76%).

NMR: DMSO <sup>1</sup>H δ (ppm): 2.9 (t,2H); 3.55 (s,3H); 4.15 (t,2H); 4.4 (d,2H); 5.95 (s,2H); 6.8-6.95 (m,3H); 7.15-7.35 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.15 (t,1H)

IR: 3272,1705,1664,1635,1501,1254,1041,751,698 cm<sup>-1</sup>

m.p. = 183°C

10 HPLC: 99.7%

**Example 16: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

**Step 1: Methyl 3-(4-methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

15 The product is obtained with a yield of 61.3% (0.750g) according to the procedure of Step 1 of Example 15, but using 4-methoxybenzyl isocyanate:

NMR: DMSO <sup>1</sup>H δ (ppm): 3.7 (s,3H); 3.8 (s,3H); 5.0 (s,2H); 6.8-6.85 (m,2H); 7.2-7.3 (m,3H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.9 (bs,1H)

**Step 2: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

20

The product from the preceding Step 1 is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.680 g of the desired compound (yield :94.8%).

NMR: DMSO <sup>1</sup>H δ (ppm): 3.7 (s,3H); 5.0 (s,2H); 6.8-7.9 (m,2H); 7.2-7.3 (m,3H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.8 (s,1H); 13.1 (bs,1H)

25

**Step 3: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**



The product is obtained with a yield of 79.9% (0.220g) according to the procedure of Example 9, using 200 mg (0.6 mmol) of the compound obtained in the preceding Step 2 and piperonylamine. The crude product is solidified in dichloromethane.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.7 (s,3H); 4.35 (d,2H); 5.0 (s,2H); 5.95 (s,2H); 6.75-6.9 (m,5H); 7.2-7.3 (m,3H); 8.1 (d,1H); 8.5 (s,1H); 9.1 (t,1H); 11.75 (s,1H)

IR: 1720,1648,1634,1504,1442,1300,1250,1036,766  $\text{cm}^{-1}$

m.p. = 252°C

HPLC: 96.2%

**Example 17: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The alkylation with methyl iodide of the product obtained in Example 16 is carried out using the procedure described in Example 15, Step 4. After crystallization from ether, 0.080 g of the product is obtained (yield : 70.4%).

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.4 (d,2H); 5.05 (s,2H); 5.95 (s,2H); 6.8-6.95 (m,5H); 7.3 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.2 (t,1H)

IR: 3265,1704,1662,1634,1504,1443,1320,1248,1040,771  $\text{cm}^{-1}$

m.p. = 178°C

HPLC: 99.2%

**Example 18: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide**

**Step 1: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-methoxybenzyl)amide**

The product is obtained with a yield of 82% (0.270g) according to the procedure of Example 9, using 240 mg (0.74 mmol) of the compound obtained in Step 2 of Example 16 and 4-methoxybenzylamine

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.7 (2s,6H); 4.4 (d,2H); 5.0 (s,2H); 6.8-6.95 (m,4H); 7.2-7.35 (m,5H); 8.15 (d,2H); 8.5 (s,1H); 9.15 (t,1H); 11.75 (bs,1H)

**Step 2: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide**

The product is obtained with a yield of 94.4% (0.260g) according to the procedure of Example 15 Step 4, using the compound obtained in the preceding in Step 1.

5     **NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.6 (s,3H); 3.7 (dd,6H); 4.45 (d,2H); 5.1 (s,2H); 6.8-6.95 (m,4H); 7.25-7.40 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

**IR:** 1705,1655,1641,1614,1510,1247,1175,1033  $\text{cm}^{-1}$

**m.p.** = 195°C

**HPLC:** 99.5%

10     **Example 19: 3-(1-Naphth-1-ylethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained according to the procedure of Example 16, Step 1 to 3, using 1-(1-naphthyl)ethyl isocyanate in the Step 1.

15     **NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 1.95 (d,3H); 4.35 (d,2H); 6.0 (s,2H); 6.7-6.8 (m,2H); 6.8-6.9 (m,2H); 7.2 (d,1H); 7.4-7.5 (m,2H); 7.6 (t,1H); 7.85-8.0 (m,5H); 8.10 (d,1H); 8.45 (s,1H); 9.10 (t,1H); 11.6 (bs,1H)

**Example 20: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

20     **Step 1: Dimethyl 4-(3-pyrid-4-ylmethylureido)isophthalate**

The product is obtained with a yield of 94.2% according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 4-pyridine methylamine.

25     **NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.8 (s,3H); 3.9 (s,3H); 4.3 (d,2H); 7.30-7.35 (m,2H); 8.0-8.1 (m,1H); 8.4 (t,1H); 8.5-8.6 (m,4H); 10.3 (s,1H)

**Step 2: Methyl 2,4-dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-**

**carboxylate**

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the compound obtained in the preceding Step 1.

5 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.85 (s,3H); 5.1 (s,2H); 7.20-7.30 (m,3H); 8.2 (d,1H); 8.4-8.5 (m,3H); 11.95 (bs,1H)

**Step 3: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The product is obtained according to the procedure of Step 2-4 of Preparation B, using the compound obtained in the preceding Step 2.

10 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 5.1 (s,2H); 7.20-7.30 (m,3H); 8.2 (d,1H); 8.4-8.5 (m,3H); 11.9 (s,1H); 13.1 (bs,1H)

**Step 4: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

15 The product is obtained with a yield of 26.7% (0.850 g) according to the procedure of Example 1, using the compound obtained in the preceding Step 3 and piperonylamine. After filtering off an insoluble material, the dimethylformamide is removed under vacuum. The residue is solidified in dichloromethane.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5  $R_f$  = 0.40

20 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.40 (d,2H); 5.0 (s,2H); 5.95 (s,2H); 6.80-6.9 (m,3H); 7.20-7.30 (m,3H); 8.1-8.2 (m,1H); 8.4-8.5 (m,3H); 9.1 (t,1H); 11.8 (s,1H)

IR: 3267,1713,1645,1626,1444,1313,1040,920,769  $\text{cm}^{-1}$

m.p. = 291.2°C

HPLC: 87.7%

**Example 21: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide**  
25

**Step 1: Methyl N-benzyl-6-(3-thien-2-ylmethylureido)isophthalate**

The product is obtained according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 2-thiophene methylamine.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.8 (s,3H); 3.9 (s,3H); 4.5 (d,2H); 6.9-7.0 (m,2H); 7.4 (m,1H);  
5 8.0-8.05 (m,1H); 8.4 (t,1H); 8.5 (s,1H); 8.6-8.65 (m,1H); 10.15 (s,1H)

**Step 2: Methyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the  
10 compound obtained in the preceding Step 1.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.8 (s,3H); 5.25 (s,2H); 6.9 (d,1H); 7.1 (s,1H); 7.25 (d,1H); 7.4 (d,1H); 8.1-8.15 (m,1H); 8.5 (s,1H); 11.9 (bs,1H)

**Step 3: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The product is obtained according to the procedure of Step 2-4 of Preparation B, using the  
15 compound obtained in the preceding Step 2.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 5.25 (s,2H); 6.95 (d,1H); 7.15 (d,1H); 7.2-7.3 (m,1H); 7.4 (d,1H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.9 (s,1H); 13.1 (bs,1H)

**Step 4: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide**

The product is obtained with a yield of 61.9% (0.160 g) according to the procedure of  
20 Example 1, using the compound obtained in the preceding Step 3 and benzylamine.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5  $R_f$  = 0.8

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.50 (d,2H); 5.2 (s,2H); 6.90-7.4 (m,9H); 8.15 (d,1H); 8.6  
25 (s,1H); 9.2 (t,1H); 11.8 (s,1H)

IR: 3185,1730,1646,1633,1512,1446,1292,1260,845,763  $\text{cm}^{-1}$

m.p. = 264.8°C

HPLC: 99.5%

**Example 22: 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid benzylamide**

5 The product is obtained with a yield of 87% (0.090 g) according to the procedure of Step 4 of Example 15, using the compound obtained in the Example 21.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.8

NMR: DMSO <sup>1</sup>H δ (ppm): 3.6 (s,3H); 4.50 (d,2H); 5.3 (s,2H); 6.90-7.0 (m,1H); 7.2-7.5 (m,7H); 7.55 (d,1H); 8.3 (d,1H); 8.7 (s,1H); 9.25 (t,1H)

IR: 3257,1704,1657,1637,1513,1480,1325,1251,829,787 cm<sup>-1</sup>

10 m.p. = 223.7°C

HPLC: 99.9%

**Example 23: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

15 The product is obtained with a yield of 59% (0.170 g) according to the procedure of Example 1, using the compound obtained in Step 3 of Example 21 and piperonylamine. The crude product is solidified in dichloromethane:

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.4

20 NMR: DMSO <sup>1</sup>H δ (ppm): 4.40 (d,2H); 5.25 (s,2H); 6.0 (s,2H); 6.75-7.0 (m,4H); 7.1 (s,1H); 7.25 (d,1H); 7.40 (d,1H); 8.2 (d,1H); 8.55 (s,1H); 9.20 (t,1H); 11.8 (s,1H)

IR: 3185,1727,1632,1502,1445,1300,1259,1040,936,846,765 cm<sup>-1</sup>

m.p. = 270.1°C

HPLC: 95.2%

**Example 24: 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

25

The product is obtained with a yield of 79.7% (0.085 g) according to the procedure of Step 4 of Example 15, using the compound obtained in the Example 23.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.8

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.6 (s,3H); 4.40 (d,2H); 5.30 (s,2H); 6.0 (s,2H); 6.8–7.0 (m,4H); 7.2 (d,1H); 7.40 (d,1H); 7.5–7.6 (m,1H); 8.2–8.30 (m,1H); 8.6 (s,1H); 9.20 (t,1H)  
IR: 3251,1705,1659,1635,1501,1446,1328,1253,1041,926,784  $\text{cm}^{-1}$   
m.p. = 224.2°C

5 HPLC: 99.8%

**Example 25: 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

10 The product is obtained with a yield of 67.8% (0.170 g) according to the procedure of Example 15 Steps 1 to 3, using in the first step the compound obtained in the Preparation A and 4-chlorobenzyl isocyanate. The product is obtained after solidification in dichloromethane.

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.35 (t,2H); 5.1 (s,2H); 5.95 (s,2H); 6.75–6.9 (m,3H); 7.25 (d,1H); 7.35 (s,4H); 8.15 (d,1H); 8.5 (s,1H); 9.15 (t,1H); 11.8 (bs,1H)  
IR: 3265,1734,1653,1633,1504,1440,1254,1041,811,761  $\text{cm}^{-1}$   
m.p. = 290°C  
HPLC: 99.2%

20 **Example 26: 3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 88.9% (0.085 g) according to the procedure of Example 15 Step 4, using the compound obtained in Example 25. The product is isolated after crystallization in ether.

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.40 (t,2H); 5.15 (s,2H); 5.95 (s,2H); 6.75–6.9 (m,3H); 7.35 (s,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H)  
IR: 3249,1704,1658,1636,1488,1251,810,753  $\text{cm}^{-1}$   
m.p. = 231°C  
HPLC: 99.6%

**Example 27: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid  
(benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained (0.035 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and monomethylamine, and in Step 4, piperonylamine for the amidation.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.50

NMR: DMSO <sup>1</sup>H δ (ppm): 3.35 (s,3H); 3.55 (s,3H); 4.40 (d,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.25 (t,1H)

IR: 1703,1649,1501,1486,1256,1037,923 cm<sup>-1</sup>

m.p. = 279°C

HPLC: 97.3%

**Example 28: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 36% (0.040 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and piperonylamine, and in Step 4, piperonylamine for the amidation.

**Step 1: Dimethyl 4-(3-benzo[1,3]dioxol-5-ylmethylureido)isophthalate**

NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 3.9 (s,6H); 4.4 (s,2H); 5.1 (t,1H); 6.70-6.85 (m,3H); 6.95 (s,2H); 8.1-8.2 (m,1H); 8.6-8.7 (m,2H); 10.6 (bs,1H)

**Step 2: Methyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

NMR: DMSO <sup>1</sup>H δ (ppm): 3.8 (s,3H); 5.0 (s,2H); 5.9 (s,2H); 6.8 (s,2H); 6.9 (s,1H); 7.25 (d,1H); 8.15 (d,1H); 8.5 (s,1H); 11.8 (bs,1H)

**Step 3: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 5.0 (s,2H); 6.0 (s,2H); 6.8 (s,2H); 6.9 (s,1H); 7.3 (d,1H); 8.2 (d,1H); 8.5 (s,1H); 11.85 (s,1H); 13.05 (bs,1H)

**Step 4: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

5 TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5

$R_f$  = 0.70

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.40 (s,2H); 5.0 (s,2H); 5.9 (s,4H); 6.75-6.95 (m,6H); 7.20-7.30 (m,1H); 8.05-8.15 (m,1H); 8.45-8.55 (m,1H); 9.1 (m,1H); 10.3 (m,1H)

IR: 3271,1739,1649,1630,1503,1440,1250,1041,926,759  $\text{cm}^{-1}$

10 m.p. = 245.2°C

HPLC: 81.5%

**Example 29: 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

15 The product is obtained with a yield of 40.5% (0.050 g) according to the procedure of Example 15 Step 4, using the compound obtained in the Example 28.

TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90/10  $R_f$  = 0.80

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.35 (s,2H); 5.0 (s,2H); 6.0 (s,4H); 6.80-7.0 (m,6H); 7.5 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.15-9.2 (m,1H)

20 IR: 3302,1703,1663,1630,1490,1247,1041,929,807,785  $\text{cm}^{-1}$

m.p. = 197.5°C

HPLC: 100%

**Example 30: 3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

25 0.150 g (0.35 mmol) of compound of Example 2, and then 3 ml of anhydrous DMF are introduced into a stirred round-bottomed flask protected from moisture. 0.075 g



(0.525 mmol) of  $K_2CO_3$  is added to the stirred solution. The mixture is stirred for 15 minutes and 0.273 g (0.14 ml, 1.75 mmol) of iodoethane is then added. Stirring is continued for about 1 hour. After removing the solvent under vacuum, the residue is dissolved in 50 ml of dichloromethane and washed with 2x 50 ml of  $H_2O$ . After drying over  $Na_2SO_4$  and concentration under vacuum, the product is crystallized from 8 ml of acetonitrile. The product is obtained as follows:

Weight: 0.070 g Yield = 43.7%

TLC:  $CH_2Cl_2/MeOH$  95/5  $R_f$  = 0.70

NMR: DMSO  $^1H$   $\delta$  (ppm): 1.25 (t,3H); 4.2 (q,2H); 4.4 (d,2H); 5.15 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.65 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.15 (t,1H)

IR: 1701,1658,1633,1506,1488,1458,1246,1217,1038,926,803  $cm^{-1}$

m.p. = 176.5°C

HPLC: 99%

**Example 31: 3-Benzyl-1-cyclopropylmethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 76.8% (0.130 g) according to the procedure of Example 30, using cyclopropylmethyl bromide. The product is obtained after solidification in diisopropyl ether.

TLC:  $CH_2Cl_2/MeOH$  95/5  $R_f$  = 0.70

NMR: DMSO  $^1H$   $\delta$  (ppm): 0.4-0.55 (m,4H); 1.25 (m,1H); 4.1 (d,2H); 4.35 (d,2H); 5.15 (s,2H); 5.95 (s,2H); 6.85 (m,3H); 7.3 (m,5H); 7.7 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

IR: 1703,1656,1641,1504,1467,1307,1261,1241,1043,936,845,748  $cm^{-1}$

m.p. = 184.4°C

HPLC: 97.2%

**Example 32: 3-Benzyl-1-isobutyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 35.3% (0.060 g) according to the procedure of Example 30, using isobutyl bromide.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.65

NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 1.0 (d,6H); 2.15 (m,1H); 4.0 (d,2H); 4.5 (d,2H); 4.25 (s,2H);  
5 5.95 (s,2H); 6.55 (m,1H); 6.8 (m,3H); 7.25 (m,4H); 7.45 (d,2H); 8.25 (t,1H); 8.45 (s,1H)

IR: 1705,1660,1643,1548,1502,1456,1303,1260,1245,1043,923 cm<sup>-1</sup>.

m.p. = 146.0°C

HPLC: 96.8%

10 **Example 33: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

**Step 1: Methyl 1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**  
0.870 g (2.7 mmol) of compound obtained in Step 1 of Preparation C, 20 ml of benzene and 2.1 g (16.1 mmol) of AlCl<sub>3</sub> are maintained at 50°C for 7 hours. After cooling, the  
15 medium is precipitated on a water/ice mixture. The insoluble material is dissolved in dichloromethane and purified by flash chromatography, eluting with a gradient of CH<sub>2</sub>Cl<sub>2</sub>/acetone. 0.510 g of the desired compound is obtained

**Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

20 The saponification of the compound obtained in the preceding Step 1 is carried out with LiOH in a dioxane/H<sub>2</sub>O mixture as for the preceding examples. Amidation with piperonylamine gives 0.160 g of the desired product.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.45

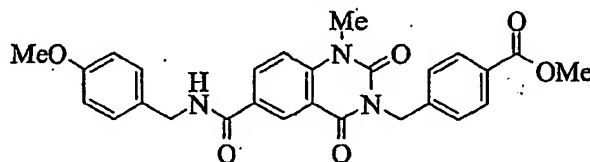
NMR: DMSO <sup>1</sup>H δ (ppm) 3.45 (s,3H); 4.4 (d,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.5  
25 (d,1H); 8.25 (d,1H); 8.55 (s,1H); 9.2 (t,1H); 11.7 (s,1H)

IR: 3290,1697,1635,1503,1484,1324,1258,1040,844 cm<sup>-1</sup>

m.p. = 279°C

HPLC: 98.7%

**Example 34: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**



**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid  
4-methoxy-benzylamide:**

Preparation identical to that of Example 33, using 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) 3.50 (s,3H); 7.5 (d,1H); 8.20 (d,1H); 8.50 (s,1H); 11.75 (bs,1H); 13.1 (bs,1H)) and 4 methoxy-benzylamine in DMF with TOTU and DIPEA. The product is obtained as follows:

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20 (d,1H); 8.55 (s,1H); 9.20 (t,1H); 11.65 (bs,1H);

**Step 2: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

0.8 g ( 2.36 mmoles) of the product obtained in the preceding Step 1 and 8 ml anhydrous DMF are stirred with 1.15 g (3.54 mmol) of cesium carbonate. Stirring is continued for 15 minutes and then 0.81 g (3.54 mmol) of methyl-4-(bromomethyl)benzoate is added. The mixture is maintained at 90°C for 1h15min and then stirred overnight. 15ml of water are added and then extracted with dichloromethane. The organic phase is washed with water and concentrated to dryness on a rotavapor. The product obtained is purified with flash chromatography eluting with a gradient of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  to provide 0.220 g of the desired product.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.85

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 3.85 (s,3H); 4.4 (d,2H); 5.25 (s,2 H); 6.9 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.55 (d,1H); 7.9 (d,2H); 8.25 (dd,1H); 8.6 (s,1H); 9.2 (t,1H)

IR : 3387,1709,1658,1642,1508,1286,1248,1110,1032,835,750  $\text{cm}^{-1}$

m.p = 189.2 °C

HPLC : 96.5 %

**Example 35: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid**

0.16g (3.3 mmol) of the product obtained in Example 34 is hydrolysed in a mixture of 1.2 ml of dioxane and 4.2 ml of water with 28mg of LiOH monohydrate. The mixture is maintained at reflux for 10 minutes to complete the reaction. After acidification at pH 1 with concentrated HCl, the precipitate is filtered off to provide 0.120 g of the desired compound.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.4 (d,2H); 5.20 (s,2 H); 6.9 (d,2H); 7.25 (d,2H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (dd,1H); 8.65 (s,1H); 9.2 (t,1H) 12.9 (bs,1H)

IR : 3378,1702,1658,1645,1616,1506,1297,1248,1125,839,788,751 cm<sup>-1</sup>.

m.p = 262.5 °C

HPLC : 100 %

**Example 36: 1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

0.100 g (0.28 mmol) of compound of Example 33 and 1 ml of anhydrous DMF are stirred with 0.060 g (0.42 mmol) of K<sub>2</sub>CO<sub>3</sub>. The mixture is maintained for 15 min, followed by addition of 0.085 g (0.42 mmol) of cinnamyl bromide. The mixture is maintained at 70°C for 2 hours. After concentration under vacuum, the residue is taken up in dichloromethane, washed with H<sub>2</sub>O and then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent is removed and the product is purified by flash chromatography, eluting with a 95/5 gradient of CH<sub>2</sub>Cl<sub>2</sub>/MeOH. A solidification in ether provides 0.070 g (yield=51%) of the desired compound.

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.46

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 4.4 (d,2H); 4.75 (d,2H); 6.0 (s,2H); 6.3-6.4 (m,1H); 6.6 (d,1H); 6.80-6.95 (m,3H); 7.2-7.35 (m,3H); 7.4 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H)

IR: 1659,1643,1503,1477,1246,754 cm<sup>-1</sup>

m.p. = 174°C

HPLC: 98.4%

**Example 37: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

A mixture of 0.5 g (1.7 mmol) of the compound of Preparation B, 0.44 g (1.7 mmol) of triphenylphosphine and 0.44 ml (4.3 mmol) of benzyl alcohol is stirred in 20 ml of THF. A solution of 0.27 ml (1.7 mmol) of DEAD in 10 ml of THF is added dropwise with stirring. Stirring is continued overnight at room temperature. The precipitate formed is filtered through Celite and the filtrate is concentrated under vacuum. The residue is dissolved in 50 ml of ethyl acetate and washed successively with H<sub>2</sub>O and then with saturated NaCl solution. After drying over MgSO<sub>4</sub> and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum to provide 0.190 g (yield = 29%) of the desired crystalline compound.

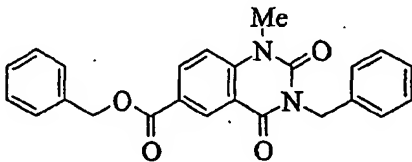
MS: m/z 387.2 (M+H)<sup>+</sup>

NMR: DMSO <sup>1</sup>H δ (ppm): 5.06 (s,2H); 5.34 (s,2H); 7.22-7.46 (m,10H); 8.20 (d,1H); 8.48 (s,1H); 11.89 (s,1H)

CHN (C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>) calc (%): C = 71.49, H = 4.70, N = 7.25

Found (%): C = 71.28, H = 4.94, N = 7.11

**Example 38: Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**



0.084 g (0.217 mmol) of the product of Example 37 is stirred with anhydrous THF in apparatus protected from moisture and under an inert atmosphere. 0.14 ml of 1.6M BuLi in hexane (0.224 mmol) is introduced. The mixture is stirred for 10 minutes, followed by addition of 0.04 ml (0.642 mmol) of methyl iodide. The THF is removed under vacuum. The residue is dissolved in EtOAc and washed successively with H<sub>2</sub>O and then with

saturated NaCl solution. After drying over  $\text{MgSO}_4$  and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum. The pale yellow product is solidified in ether:

- 5 **Weight:** 0.049 g **Yield =** 56% **MS:**  $m/z$  401.2 (M+H)<sup>+</sup>  
**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.31 (s,3H); 5.12 (s,2H); 5.37 (s,2H); 7.21-7.60 (m,11H); 8.28 (d,1H); 8.58 (s,1H)  
**CHN** ( $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4$ ) **calc (%)**: C = 71.99, H = 5.03, N = 7.00  
**Found (%)**: C = 71.71, H = 5.25, N = 6.87

10 **Example 39: 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline  
 -6-carboxylate**

The compound is obtained according to the procedure of Example 37, but using dichloromethane as solvent, the product is obtained as follows:

- MS:**  $m/z$  388.2 (M+H)<sup>+</sup>  
 15 **NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 5.07 (s,2H); 5.41 (s,2H); 7.20-7.32 (m,6H); 7.43 (d,2H); 8.26 (d,1H); 8.53-8.58 (m,3H); 11.93 (s,1H)  
**CHN** ( $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_4 \cdot 0.3\text{H}_2\text{O}$ ) **calc (%)**: C = 67.27, H = 4.52, N = 10.70  
**found (%)**: C = 67.32, H = 4.40, N = 10.47

20 **Example 40: 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4  
 -tetrahydroquinazoline -6-carboxylate**

The compound is obtained according to the procedure of Example 37, but using the compound of Preparation C and 4-pyridylcarbinol.

- MS:**  $m/z$  402.3 (M+H)<sup>+</sup>  
**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 5.14 (s,2H); 5.42 (s,2H); 7.23-7.33 (m,5H); 7.43-  
 25 7.45 (m,2H); 7.60 (d,1H); 8.32-8.36 (m,1H); 8.57-8.64 (m,3H)  
**CHN** ( $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_4 \cdot 0.14 \text{H}_2\text{O}$ ): **calc (%)**: C = 68.39, H = 4.81, N = 10.40  
**found (%)**: C = 68.40, H = 4.71, N = 10.38

**Example 41: Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

0.100 g (0.337 mmol) of compound of Preparation B and 1 ml of anhydrous THF are placed in a round-bottomed flask protected from moisture. The suspension is stirred and  
5 0.24 g (0.150 ml, 2.025 mmol) of thionyl chloride is added. The mixture is refluxed for 1 h 30 min. After cooling, the solution is concentrated to dryness on a rotavapor. The 0.110 g of acid chloride obtained is used in the next stage without further purification.

0.080 g (0.51 mmol) of piperonyl alcohol, 1 ml of dichloromethane and 0.051 g (0.070 ml, 0.51 mmol) of triethylamine are introduced into a round-bottomed flask protected from  
10 moisture. The solution is cooled to 0°C.

The above acid chloride suspended in 2.5 ml of dichloromethane is added to the solution.

The mixture is stirred at room temperature for 48 hours. The precipitate obtained is filtered off. The 0.050 g is purified by recrystallization from acetonitrile.

**Weight:** 0.025 g **Yield** = 17%

15 **TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.85

**NMR:** DMSO <sup>1</sup>H δ (ppm): 5.1 (s,2H); 5.25 (s,2H); 6.05 (s,2H); 6.9-7.4 (m,9H); 8.2 (d,1H); 8.5 (s,1H); 11.9 (bs,1H)

**IR:** 1715,1650,1624,1446,1285,1262,1080,928,865,764 cm<sup>-1</sup>

**m.p.** = 238.5°C

20 **HPLC:** 99.7%

**Example 42: Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

The compound is obtained (0.140 g) according to the procedure of Example 41, but using the compound of Preparation C and piperonyl alcohol.

25 **TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.85

**NMR:** DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 5.15 (s,2H); 5.30 (s,2H); 6.05 (s,2H); 6.9-7.4 (m,8H); 7.6 (d,1H); 8.25 (d,1H); 8.6 (s,1H)

**IR:** 1716,1703,1659,1618,1447,1294,1227,1103, 935,813,763 cm<sup>-1</sup>

m.p. = 199.5°C

HPLC: 98.8%

**Example 43: Benzyl 1-benzyl-2,4-dioxo-3-pyrid-4-ylmethyl-1,2,3,4  
-tetrahydroquinazoline-6-carboxylate**

5 0.5 g (1.7 mmol) of compound obtained in the Step 3 of Example 20 in 15 ml of anhydrous THF is stirred and 0.2 ml (1.7 mmol) of benzyl chloride and 1.2 g (8.7 mmol) of K<sub>2</sub>CO<sub>3</sub> are added. The mixture is stirred overnight at room temperature and treated as usual to provide the desired compound.

MS: m/z 478.2 (M+H)+

10 NMR: DMSO <sup>1</sup>H δ (ppm): 5.19 (s,2H); 5.35 (s,2H); 5.39 (s,2H); 7.25-7.45 (m,13H); 8.19 (d,1H); 8.47-8.49 (m,2H); 8.62 (s,1H)

CHN (C<sub>29</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>) calc (%): C = 72.94, H = 4.85, N = 8.80

Found (%): C = 72.58, H = 4.79, N = 8.57

**Example 44: 4-Pyridylmethyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4  
-tetrahydroquinazoline-6-carboxylate**

15

0.69 g (2.3 mmol) of compound obtained in Step 3 of Example 21 is treated according to the procedure of Example 37, using 4-pyridylcarbinol. The product is obtained as follows:

MS: m/z 394.2 (M+H)+

20 NMR: DMSO <sup>1</sup>H δ (ppm): 5.21 (s,2H); 5.40 (s,2H); 6.93 (d,1H); 7.11 (m,1H); 7.28 (d,1H); 7.40 (d,1H); 7.40 (m,2H); 8.24 (d,1H); 8.49-8.59 (m,3H)

CHN (C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S·0.13 CH<sub>2</sub>Cl<sub>2</sub>·0.03 (ether))

Calc (%): C = 59.81 H = 3.86, N = 10.33;

Found (%): C = 59.79, H = 3.82, N = 10.32

**Example 45: 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4  
-tetrahydroquinazoline-6-carboxylate**

25



The compound is obtained (0.040 g) according to the procedure of example 37, but using the compound obtained in the Step 3 of Example 28 and 4-pyridylcarbinol. The product is crystallized from methanol:

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.70

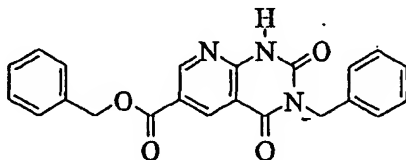
5 NMR: DMSO <sup>1</sup>H δ (ppm): 5.0 (s,2H); 5.70 (s,2H); 6.0 (s,2H); 6.85 (s,2H); 7.0 (s,1H); 7.4 (d,1H); 7.95-8.05 (m,2H); 8.3-8.35 (m,1H); 8.60 (s,1H); 8.8-8.95 (m,2H); 12.0 (m,1H)

IR: 1710,1670,1622,1501,1440,1279,1236,1041,923,764 cm<sup>-1</sup>

m.p. = 204.4°C

HPLC: 92.4%

10 **Example 46: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate**



**Step 1: 3-Benzyl-6-methyl-1H-pyrido[2,3-*d*]pyrimidine-2,4-dione**

20 g (111 mmol) of ethyl 2-amino-5-methylnicotinate and 200 ml of pyridine are brought to reflux. 13.7 ml (111 mmol) of benzyl isocyanate are added. Refluxing is continued  
15 overnight. After cooling, the precipitate is filtered off and washed with 2x100 ml of ethanol and 2x 100 ml of ether.

Weight: 10 g in two crops Yield = 34%

TLC: CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10 R<sub>f</sub> = 0.5

20 NMR: DMSO <sup>1</sup>H δ (ppm): 2.2 (s,3H); 5.0 (s,2H); 7.15-7.35 (m,5H); 8.1 (s,1H); 8.5 (s,1H)

m.p. = 279°C

HPLC: 97%

**Step 2: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid**

25 3.0 g (11.2 mmol) of the product of the preceding Step 1, 100 ml of H<sub>2</sub>O, 7.1 g (44.9 mmol) KMnO<sub>4</sub> and 10 ml of NMP are introduced into a round-bottomed flask. The reaction medium is refluxed overnight. The medium is filtered while hot. The filtrate

crystallizes after cooling. After filtering off the new precipitate, the filtrate is treated with 40 ml of Amberlite IR 120 (+) resin. The resin and acid mixture is filtered and the acid is extracted by washing with a 70/30 mixture of  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ . The solvent is removed under vacuum to provide 0.32 g of a white solid (yield = 10%).

5 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 5.0 (s,2H); 7.15-7.25 (m,5H); 8.65 (s,1H); 9.1 (s,1H); 12.4 (s,1H)

**Step 3: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate**

The esterification of the compound of the preceding Step 2 is carried out by the procedure described in Example 37, using benzyl alcohol.

After solidification in methanol, 0.040 g of the desired product is obtained (yield = 31%):

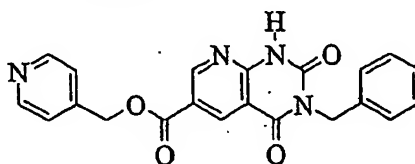
TLC:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5  $R_f$  = 0.8

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 5.2 (s,2H); 5.4 (s,2H); 7.2-7.6 (m,10H); 9.05 (s,1H); 9.3 (s,1H); 10.9 (s,1H)

15 m.p. = 223°C

HPLC: 93.1%

**Example 47: 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate.**



20 The compound is obtained with a yield of 20% (0.050 g) according to the procedure described in Example 37, but using the compound obtained in the Step 2 of example 46 and 4-pyridylcarbinol.

TLC:  $\text{EtOAc}/\text{NH}_4\text{OH}$  99/1  $R_f$  = 0.6

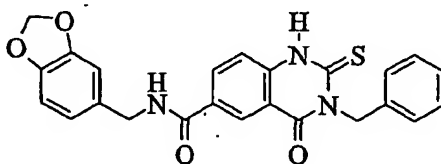
NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 5.05 (s,2H); 5.4 (s,2H); 7.15-7.41 (m,5H); 7.45 (d,2H); 8.55 (d,2H); 8.7 (s,1H); 9.15 (s,1H); 12.55 (s,1H)

25

m.p. = 280°C

HPLC: 97%

**Example 48: 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid  
(benzo[1,3]dioxol-5-ylmethyl)amide**



The synthesis is carried out according to Synthetic Scheme 1, using benzyl isothiocyanate during the cyclization to the 4-oxo-2-thioxoquinazoline. After saponification and amidation with piperonylamine, the expected compound is obtained.

**Weight:** 0.100 g **TLC:** CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5 R<sub>f</sub> = 0.64

**NMR:** DMSO <sup>1</sup>H δ (ppm): 4.4 (d,2H); 5.65 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.45 (d,1H); 8.2 (d,1H); 8.55 (s,1H); 9.2 (t,1H); 13.2 (bs,1H)

**IR:** 1698,1636,1619,1528,1446,1194,1037,768

**m.p.** = 249°C

**HPLC:** 97.2%

**Example 49: 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

Into a stirred round-bottomed flask protected from moisture, 0.7 g (1.44 mmol) of compound of Example 34 and 70 ml of anhydrous dichloromethane are introduced. The mixture is stirred and 1.4 ml (14.4 mmol) of BBr<sub>3</sub> in 7 ml of dichloromethane are added dropwise. After 2 hours of stirring at room temperature the reaction is complete. After an usual treatment, 0.280 g of the desired product is obtained. (yield = 42%).

**TLC:** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.15

**NMR:** DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 4.35 (d,2H); 5.2 (s,2H); 6.65 (d,2H); 7.10 (d,2H); 7.40 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.15 (t,1H); 9.2 (s,1H); 12.8 (bs,1H)

**IR:** 3403, 2553, 1697, 1658, 1615, 1507, 1482, 1423, 1247, 1109, 829, 752 cm<sup>-1</sup>

**M.P.** = 174.0 °C

**HPLC:** 97.06 %

**Example 50 : 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro  
quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

0.3 g (0.64 mmol) of the compound of Example 35 is treated with a 2M solution of dimethylamine in THF according to the procedure described in Example 1. The crude product is purified by chromatography on silica gel and concretized in ether to provide 0.160 g of the desired compound (yield : 49.9%).

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

NMR: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 2.90 (s, 3H); 3.05 (s, 3H); 3.60 (s, 3H); 3.80 (s, 3H); 4.60 (d, 2H); 5.25 (s, 2H); 6.60 (t, 1H); 6.85 (d, 2H); 7.3 (m, 5H); 7.45 (d, 2H); 8.25 (d, 1H); 8.50 (s, 1H).

IR : 3378, 1710, 1654, 1641, 1618, 1508, 1476, 1246, 752 cm<sup>-1</sup>

M.P. = 189 °C

HPLC : 97 %

**Example 51 : 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro  
-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of Example 50 but using methylamine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.55

NMR: DMSO <sup>1</sup>H δ (ppm): 2.75 (d, 3H); 3.55 (s, 3H); 3.70 (s, 3H); 4.40 (d, 2H); 5.20 (s, 2H); 6.85 (d, 2H); 7.25 (d, 2H); 7.35 (d, 2H); 7.55 (d, 1H); 7.75 (d, 2H); 8.25 (q, 1H); 8.35 (d, 1H); 8.60 (s, 1H); 9.2 (t, 1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm<sup>-1</sup>

M.P. = 255.1 °C

HPLC : 97.0 %

**Example 52: 3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic  
acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-allyl bromide.

5 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.8 (s,3H); 4.4 (d,2H); 4.55 (d,2H); 5.10-5.20 (m,2H); 5.80-5.95 (m,1H); 6.9 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.25 (t,1H)

IR : 1703, 1642, 1615, 1508, 1477, 1246, 765  $\text{cm}^{-1}$

M.P. = 207  $^{\circ}\text{C}$

HPLC : 98.9 %

10 **Example 53 : 1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1(2-bromoethyl)pyrrole.

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.15 (m,2H); 4.25 (m,2H); 4.40 (d,2H); 5.90 (s,2H); 6.7 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.55 (s,1H); 9.2 (t,1H)

IR : 3338, 1708, 1655, 1640, 1508, 1478, 1251, 117, 1032, 835, 734  $\text{cm}^{-1}$

M.P. = 147  $^{\circ}\text{C}$

20 HPLC : 96.6 %

**Example 54: 1-Methyl-2,4-dioxo-3-(prop-2-ynyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and prop-2-ynyl bromide.

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.15 (s,1H); 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.70 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H).

IR : 3265, 1710, 1667, 1635, 1501, 1326, 1249, 1036, 825, 783, 752  $\text{cm}^{-1}$

M.P. = 206 °C

HPLC : 97.7 %

5      **Example 55: 1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-3-methyl-but-2-ene.

10      NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 1.65 (s,3H); 1.75 (s,3H); 3.50 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.55 (d,2H); 5.20 (t,1H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 3282, 1705, 1659, 1634, 1500, 1314, 1246, 826  $\text{cm}^{-1}$

M.P. = 187 °C

15      HPLC : 96.9 %

**Example 56: 1-Methyl-2,4-dioxo-3-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-(bromomethyl)pyridine.

20      NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (m,3H); 7.35 (d,1H); 7.60 (d,1H); 7.70 (m,1H); 8.25 (d,1H); 8.40 (d,1H); 8.60 (s,1H); 9.2 (t,1H)

IR : 1702, 1658, 1643, 1618, 1508, 1476, 1331, 1248, 751  $\text{cm}^{-1}$

25      M.P. = 156 °C

HPLC : 99.5 %

**Example 57: 3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-chloro-acetamide.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.50 (s,2H); 6.90 (d,2H); 7.20 (s,1H); 7.25 (d,2H); 7.55 (d,1H); 7.65 (s,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 1655,1531,1508,1477,1303,1249,752  $\text{cm}^{-1}$

M.P. = 269 °C

HPLC : 99.2 %

**Example 58: 1-Methyl-2,4-dioxo-3-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the-Step 1 of the Example 34 and 3-(bromomethyl)pyridine.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.20-7.40 (m,3H); 7.55 (d,1H); 7.75 (d,1H); 8.25 (m,1H); 8.45 (d,1H); 8.60 (m,2H); 9.20 (t,1H)

IR : 1699, 1660, 1615, 1500, 1479, 1249, 1032, 752, 712  $\text{cm}^{-1}$

M.P. = 140 °C

HPLC : 89.6 %

**Example 59 : 1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-bromomethyl-1-methyl-piperidine

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 0.85-1.00 (m,1H); 1.30-1.45 (m,1H); 1.55-2.05 (m,5H); 2.10 (s,3H); 2.60 (m,2H); 3.55 (s,3H); 3.75 (s,3H); 3.85 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 2926, 1655, 1641, 1508, 1247, 788  $\text{cm}^{-1}$

5 M.P. = 174  $^{\circ}\text{C}$

HPLC : 99.3 %

**Example 60 : 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

10 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)benzonitrile

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.45-7.60 (m,3H); 7.75 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

15 IR : 3411, 2216, 1708, 1649, 1616, 1251, 839, 765  $\text{cm}^{-1}$

M.P. = 222  $^{\circ}\text{C}$

HPLC : 97.2 %

**Example 61 : 3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

20 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-benzonitrile.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.45 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (m,2H); 7.70 (m,2H); 7.80 (s,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718  $\text{cm}^{-1}$

M.P. = 201  $^{\circ}\text{C}$



HPLC : 97.1 %

**Example 62 : 3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but  
5 using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-2-methoxy-ethane.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.25 (s,3H); 3.55 (m,5H); 3.70 (s,3H); 4.15 (t,2H); 4.40 (d,2H);  
6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3274, 1709, 1660, 1633, 1514, 1249, 1030, 823  $\text{cm}^{-1}$

10 M.P. = 200 °C

HPLC : 99.2 %

**Example 63 : 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but  
15 using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-1-methoxyphenyl.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,6H); 4.40 (d,2H); 5.10 (s,2H); 6.75-6.90  
(m,5H); 7.15-7.30 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3387, 1704, 1657, 1640, 1616, 1509, 1250, 766  $\text{cm}^{-1}$

20 M.P. = 154 °C

HPLC : 99.4 %

**Example 64: 3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but  
25 using as substrates the compound obtained in the Step 1 of the Example 34 and bromomethylcyclopropyl.

NMR: DMSO- $d_6$   $^1H$   $\delta$  (ppm): 0.40 (m,4H); 1.2 (m,1H); 3.55 (s,3H); 3.70 (s,3H); 3.85 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (m,1H); 8.60 (d,1H); 9.20 (t,1H).

IR : 3282,1703, 1657, 1634, 1502, 1258, 1028, 829, 752  $cm^{-1}$

M.P. = 209 °C

5 HPLC : 98.2 %

**Example 65: 1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(2-bromoethyl)morpholine.

NMR: DMSO- $d_6$   $^1H$   $\delta$  (ppm): 2.40 (m,4H); 2.55 (m,2H); 3.50 (m,7H); 3.75 (s,3H); 4.10 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3419, 1707, 1656, 1612, 1506, 1475, 1246, 1111, 752  $cm^{-1}$

15 M.P. = 135 °C

HPLC : 98.5 %

**Example 66: 3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and (bromomethyl)cyclohexane.

NMR: DMSO- $d_6$   $^1H$   $\delta$  (ppm): 0.9-1.20 (m,5H); 1.5-1.85 (m,6H); 3.55 (s,3H); 3.70 (s,3H); 3.80 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (m,1H); 8.60 (s,1H); 9.20 (t,1H)

25 IR : 3378, 2918, 1703, 1654, 1640, 1508, 1478, 1329, 1244, 789, 767  $cm^{-1}$

M.P. = 183 °C

HPLC : 99.0 %

**Example 67: 1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-phenylpropyl bromide.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 1.90 (m,2H); 2.65 (t,2H); 3.50 (s,3H); 3.70 (s,3H); 4.0 (t,2H); 4.40 (d,2H); 6.85 (d,2H); 7.10-7.30 (m,7H); 7.50 (d,1H); 8.20 (m,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749  $\text{cm}^{-1}$

M.P. = 167 °C

HPLC : 98.8 %

**Example 68: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)-fluorobenzene.

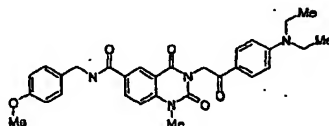
NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.1 (s,2H); 6.90 (d,2H); 7.10 (t,2H); 7.25 (d,2H); 7.40 (m,2H); 7.50 (d,1H); 8.25 (m,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749  $\text{cm}^{-1}$

M.P. = 180 °C

HPLC : 99.4 %

**Example 69: 3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-Chloro-1-(4-diethylamino-phenyl)-ethan-1-one.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 1.15 (t, 6H); 3.30-3.50 (m, 4H); 3.60 (s, 3H); 3.75 (s, 3H); 4.45 (d, 2H); 5.35 (s, 2H); 6.75 (d, 2H); 6.90 (d, 2H); 7.30 (d, 2H); 7.65 (d, 1H); 7.90 (d, 2H); 8.30 (m, 1H); 8.60 (s, 1H); 9.25 (t, 1H)

IR : 3370, 1670, 1655, 1596, 1504, 1258, 1242, 1190, 808  $\text{cm}^{-1}$

M.P. = 237  $^{\circ}\text{C}$

HPLC : 97.0 %

**Example 70: Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-acetate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 2-chloro-acetate.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 1.20 (t, 3H); 3.60 (s, 3H); 3.70 (s, 3H); 4.15 (q, 2H); 4.40 (d, 2H); 4.70 (s, 2H); 6.90 (d, 2H); 7.25 (d, 2H); 7.60 (d, 1H); 8.30 (m, 1H); 8.60 (s, 1H); 9.20 (t, 1H)

IR : 1711, 1668, 1637, 1508, 1247, 1212, 1032, 835, 752  $\text{cm}^{-1}$

M.P. = 170  $^{\circ}\text{C}$

HPLC : 97.7 %

**Example 71: 3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-bromoethan-1-ol.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50-3.65 (s, 5H); 3.70 (s, 3H); 4.05 (t, 2H); 4.40 (d, 2H); 4.80 (t, 1H); 6.90 (d, 2H); 7.25 (d, 2H); 7.50 (s, 1H); 8.25 (m, 1H); 8.60 (s, 1H); 9.25 (t, 1H)

IR : 3290, 1702, 1654, 1639, 1619, 1509, 1327, 1240, 1071, 835, 753  $\text{cm}^{-1}$

M.P. = 168 °C

HPLC : 96.7 %

**Example 72: Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionate**

5 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-bromo-propionate.

NMR: DMSO <sup>1</sup>H δ (ppm) : 2.60 (t,2H); 3.50 (s,3H); 3.60 (s,3H); 3.70 (s,3H); 4.20 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.25 (t,1H)

10 IR : 3411, 2361, 1704, 1656, 1644, 1618, 1508, 1478, 1328, 1244, 853, 766 cm<sup>-1</sup>

M.P. = 154.8 °C

HPLC : 95.1 %

**Example 73 : 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionic acid**

15

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 72.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.25

NMR: DMSO <sup>1</sup>H δ (ppm) : 2.50 (t,2H); 3.55 (s,3H); 3.70 (s,3H); 4.15 (t,2H); 4.40 (d,2H); 6.85 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.55 (s,1H); 9.15 (t,1H); 12.3 (bs,1H)

20

IR : 3395, 2353, 1701, 1656, 1639, 1508, 1478, 1244, 1040, 839, 799, 754 cm<sup>-1</sup>

M.P. = 201.5 °C

HPLC : 96.4 %

**Example 74 : Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyrate**

25

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 4-bromobutyrate.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 1.10 (t,3H); 1.90 (q,2H); 2.30 (t,2H); 3.55 (s,3H); 3.70 (s,3H);  
5 4.00 (bs,4H); 4.45 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20 (dd,1H); 8.60 (s,1H); 9.15 (t,1H)

IR : 3378, 2943, 1704, 1657, 1647, 1617, 1509, 1477, 1246, 1178, 1030, 751  $\text{cm}^{-1}$

M.P. = 138.9 °C

HPLC : 99.1 %

10 **Example 75 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyric acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 74.

15 **TLC** :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.50

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 1.80 (q,2H); 2.25 (t,2H); 3.50 (s,3H); 3.70 (s,3H); 4.0 (t,2H);  
4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.20 (t,1H);  
12.0 (bs,1H)

IR : 3346, 1691, 1651, 1637, 1512, 1234, 1248, 1178, 1024, 835, 752  $\text{cm}^{-1}$

20 **M.P.** = 165.6 °C

**HPLC** : 99.1 %

**Example 76: Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but  
25 using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-(bromomethyl)phenyl acetate

**TLC** :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s,3H); 3.60 (s,3H); 3.65 (s,2H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.10-7.35 (m,6H); 7.55 (d,1H); 8.25 (dd,1H); 8.65 (s,1H); 9.20 (t,1H)

IR : 3370, 2951, 1707, 1655, 1639, 1616, 1509, 1328, 1251, 1157, 1036, 766  $\text{cm}^{-1}$

5 M.P. = 173.2  $^{\circ}\text{C}$

HPLC : 99.0 %

**Example 77 : {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid**

10 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 76.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.50

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s,2H); 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.10-7.35 (m,6H); 7.55 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.20 (t,1H); 12.3 (bs,1H)

15 IR : 3378, 1706, 1653, 1640, 1616, 1508, 1330, 1249, 1149, 1032, 823, 766  $\text{cm}^{-1}$

M.P. = 165  $^{\circ}\text{C}$

HPLC : 96.7 %

**Example 78 : 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

20 The compound is obtained from the compound obtained in Example 77, which is transformed in situ into the acid chloride derivate by action of oxalyle chloride and then treated with a 2M solution of dimethylamine in THF.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.50

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.80 (s,3H); 3.0 (s,3H); 3.55 (s,3H); 3.60 (s,2H); 3.75 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.15 (d,2H); 7.25 (d,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3308, 2926, 1706, 1665, 1640, 1504, 1474, 1320, 1250, 1133, 1036, 834  $\text{cm}^{-1}$

M.P. = 183 °C

HPLC : 93.2 %

**Example 79 : 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

5 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-((E)-3-chloro-propenyl)-pyridine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.63

10 NMR: DMSO <sup>1</sup>H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 4.75 (d,2H); 6.40-6.50 (m,1H); 6.50-6.60 (d,1H); 6.90 (d,2H); 7.20-7.35 (m,3H); 7.55 (d,1H); 7.85 (d,1H); 8.25 (d,1H); 8.40 (s,1H); 8.60 (d,2H); 9.20 (t,1H).

IR : 3395, 1703, 1643, 1509, 1479, 1254, 761 cm<sup>-1</sup>

M.P. = 200.0 °C

HPLC : 98.7 %

15 **Example 80 : 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-((E)-3-chloro-propenyl)-pyridine.

20 TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.43

NMR: DMSO <sup>1</sup>H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 4.80 (d,2H); 6.55 (d,1H); 6.60-6.70 (m,1H); 6.90 (d,2H); 7.25 (d,2H); 7.35 (d,2H); 7.55 (d,1H); 8.25 (dd,1H); 8.45 (d,2H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3395, 1704, 1643, 1509, 1479, 1332, 1254, 980, 765 cm<sup>-1</sup>

25 M.P. = 241 °C

HPLC : 98.1 %



**Example 81 : 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro  
quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-bromomethyl-benzenesulfonamide.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.48

NMR: DMSO <sup>1</sup>H δ (ppm) : 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.30 (s,2H); 7.50 (d,2H); 7.55 (d,1H); 7.75 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm<sup>-1</sup>

M.P. = 219.0 °C

HPLC : 94.9 %

**Example 82 : 3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-  
quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the Step 1-5 to 2-5 of the preparation B using 3-(4-methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid.

NMR: DMSO <sup>1</sup>H δ (ppm): 3.20 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.15 (d,2H); 7.50-7.60 (m,3H); 7.85 (d,2H); 8.30 (dd,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3370, 1707, 1658, 1641, 1303, 1148, 783 cm<sup>-1</sup>

M.P. = 210°C

HPLC: 97.9 %

**Example 83 : 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-  
quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

**Step 1 : Methyl 3-(4-chlorosulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

Into a stirred round-bottomed flask protected from moisture, 3.2 ml (47.5 mmol) of chlorosulfonic acid are introduced. The mixture is cooled with an ice bath and 2.2 g (6.80 mmol) of compound obtained in the Step 1 of Preparation C are added slowly. After 3 hours stirring at room temperature, the reaction mixture is poured in an mixture of water and ice. The precipitate is filtered and dried to provide 1.8 g of the desired product.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s, 3H); 3.90 (s, 3H); 5.15 (s, 2H); 7.25 (m, 2H); 7.50-7.60 (m, 3H); 8.25 (dd, 1H); .60 (s, 1H).

**Step 2: Methyl 3-(4-dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

To a stirred solution of 0.4 g (0.94 mmol) of the compound obtained in the preceding Step 1 in 25 ml of dichloromethane are added 3.3 ml (66 mmol) of dimethylamine 2M in THF. After 1 hour, the reaction mixture is concentrated under vacuum. A chromatography on silica gel (dichloromethane/acetone: 98/2) provides 0.370 g (yield : 91%) of the desired product.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 2.6 (s, 6H); 3.6 (s, 3H); 3.9 (s, 3H); 5.25 (d, 2H); 7.60 (m, 3H); 7.70 (m, 2H); 8.25 (dd, 1H); 8.60 (s, 1H).

**Step 3 : 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid**

The compound is obtained according to the procedure of the Step 2-4 of Preparation B, using as substrate the compound obtained in the preceding Step 2.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 2.60 (s, 6H); 3.55 (s, 3H); 5.25 (s, 2H); 7.60 (m, 3H); 7.70 (m, 2H); 8.25 (dd, 1H); 8.60 (s, 1H); 13.20 (bs, 1H).

**Step 4: 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Example 1, but using 4-methoxybenzylamine. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.48

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.55 (s,6H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55-7.60 (m,3H); 7.60-7.70 (m,2H); 8.30 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718  $\text{cm}^{-1}$

5 M.P. = 112  $^{\circ}\text{C}$

HPLC : 94.8 %

**Example 84 : 3-[4-(2-Dimethylamino-ethylsulfamoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

10 The compound is obtained according the procedure of Steps 1 to 4 of the Example 83 using *N,N'*-dimethylethylene diamine in the Step 2. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.47

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.0-2.15 (m,6H); 2.20-2.35 (m,2H); 2.75-2.85 (m,2H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.25 (d,2H); 7.45-7.65 (m,4H); 7.65-7.80 (m,2H); 8.25 (d,1H); 8.60 (m,1H); 9.20 (m,1H).

IR : 1707, 1656, 1618, 1508, 1477, 1326, 1249, 1155  $\text{cm}^{-1}$

M.P. = 114  $^{\circ}\text{C}$

HPLC : 90.9 %

20 **Example 85 : 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

**Step 1 : Methyl 1-methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

25 The compound is obtained according the procedure of Steps 1 to 3 of the Example 83 using methylamine in the Step 2.

**Step 2 : 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

0.2 g (0,5 mmol) of the compound obtained in the preceding Step 1 is dissolved in 10 ml of dichloroethane. The solution is cooled and 3.2 ml (6.4 mmol) of trimethylaluminium 2M in toluene and 0.875 g (6.4 mmol) of 4-methoxy-benzylamine are added. The solution mixture is stirred overnight at room temperature and then 24 hours at 60°C. The solution is  
5 evaporated under vacuum and a chromatography over silica gel (dichloromethane/ether) provides 0.085 g (yield 32%) of the desired product.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

NMR: DMSO <sup>1</sup>H δ (ppm): 2.40 (d,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H);  
6.85 (d,2H); 7.25 (d,2H); 7.40 (q,1H); 7.50 (d,2H); 7.60 (d,1H); 7.70 (d,2H); 8.25 (d,1H);  
10 8.65 (s,1H); 9.2 (t,1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm<sup>-1</sup>

M.P. = 217.0 °C

HPLC : 95.0 %

15 **Example 86 : Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-(bromomethyl)benzoate.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.80

20 NMR: DMSO <sup>1</sup>H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.2 (s,2H); 6.80-6.90 (m,2H); 7.2- 7.3 (m,2H); 7.4-7.5 (m,1H); 7.5-7.6 (m,1H); 7.6-7.7 (m,1H); 7.8-7.9 (m,1H); 7.95 (s,1H); 8.30 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3254, 1729, 1705, 1659, 1637, 1502, 1299, 1249, 749 cm<sup>-1</sup>

M.P. = 193.5 °C

25 HPLC : 100 %

**Example 87 : 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 86.

**TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

**NMR**: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.90 (d,2H);  
5 7.25 (d,2H); 7.40-7.45 (m,1H); 7.5-7.65 (m,2H); 7.80 (d,1H); 7.95 (s,1H); 8.20 (d,1H);  
8.60 (s,1H); 9.2 (t,1H); 12.95 (s,1H)

**IR** : 3400, 3190, 1705, 1659, 1646, 1616, 1510, 1247, 1197, 750 cm<sup>-1</sup>

**M.P.** = 182 °C

**HPLC** : 98.8 %

10 **Example 88: (E) Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-bromocrotonate.

15 **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.75

**NMR**: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 4.75 (d,2H);  
5.9 (d,1H); 6.80-6.90 (m,2H); 6.9-6.95 (m,1H); 7.2-7.3 (m,2H); 7.55 (d,1H); 8.25 (d,1H);  
8.60 (s,1H); 9.2 (t,1H).

**IR** : 3408, 1708, 1644, 1617, 1507, 1477, 1280, 1248, 1036, 765 cm<sup>-1</sup>

20 **M.P.** = 107.9 °C

**HPLC** : 96.2 %

**Example 89 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoic acid**

25 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 88.

**TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.30 (d,2H); 4.70 (d,2H); 5.70-5.80 (m,1H); 6.70-6.85 (m,1H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20-8.25 (m,1H); 8.60 (s,1H); 9.2 (t,1H); 12.3 (bs,1H)

IR : 3409, 1700, 1644, 1617, 1506, 1304, 1248, 767  $\text{cm}^{-1}$

5 M.P. = 245.5  $^{\circ}\text{C}$

HPLC : 91.3 %

**Example 90 : Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylate**

10 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-(chloromethyl)-2-furoate.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.60

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.55 (d,1H); 6.85 (d,2H); 7.25 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

15 IR : 3249, 1711, 1664, 1636, 1503, 1446, 1299, 1250, 1148, 1023, 824, 765  $\text{cm}^{-1}$

M.P. = 195.5  $^{\circ}\text{C}$

HPLC : 99.2 %

**Example 91 : 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylic acid**

20 The compound is obtained by hydrolysis, in the presence of  $\text{K}_2\text{CO}_3$  in a mixture of dioxane/water, of the compound of the Example 90.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.10

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (s,2H); 5.20 (s,2H); 6.50 (s,1H); 6.90 (d,2H); 7.10 (s,1H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H);  
25 13.05 (bs,1H).

IR : 1711, 1661, 1618, 1505, 1477, 1326, 1248, 1141, 1024, 968, 824, 787  $\text{cm}^{-1}$

M.P. = 198  $^{\circ}\text{C}$

HPLC : 100.0 %

**Example 92: Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-bromomethyl-thiophene-2-carboxylate. This compound is obtained according to the procedure described in *J. Med. Chem.*, 1998, 41 (1), 74-95.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.20

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.30 (s,2H); 6.90 (d,2H); 7.15 (d,1H); 7.25 (d,2H); 7.55 (d,1H); 7.60 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3249, 1707, 1660, 1635, 1515, 1326, 1294, 1092, 1036, 625, 749 cm<sup>-1</sup>

M.P. = 200.5°C

HPLC : 91.5 %

**Example 93 : 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylic acid**

The compound is obtained by hydrolysis, in the presence of K<sub>2</sub>CO<sub>3</sub> in a mixture of dioxane/water, of the compound of the Example 92.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.25

NMR: DMSO <sup>1</sup>H δ (ppm) : 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.30 (s,2H); 6.90 (d,2H); 7.15 (d,1H); 7.25 (d,2H); 7.55 (m,2H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H); 13.0 (m,1H).

IR : 3241, 1705, 1662, 1632, 1541, 1325, 1246, 1032, 921, 826, 783 cm<sup>-1</sup>

M.P. = 198.5 °C

HPLC : 92.2 %

**Example 94 : 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-nitrobenzyl bromide.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f = 0.47$

5 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50-7.65 (m,3H); 8.15 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 1706, 1661, 1618, 1513, 1477, 1345, 1248, 752  $\text{cm}^{-1}$

M.P. = 129.0  $^{\circ}\text{C}$

HPLC : 100 %

10 **Example 95 : 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

1 g (2.1 mmol) of the compound of Example 94 is hydrogenated with Pd/C in a mixture of dichloromethane/methanol 80/20 v/v. After 2 hours of stirring under hydrogen atmosphere, the reaction mixture is filtered. The solvent is removed under vacuum and the crude  
15 product is concretized from a mixture of dichloromethane/ether to provide 0.800 g of the desired compound (yield: 85.8%).

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f = 0.19$

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 4.90-5.05 (m,4H); 6.45 (d,2H); 6.90 (d,2H); 7.05 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2  
20 (t,1H).

IR : 3387, 1701, 1647, 1615, 1511, 1478, 1245, 789  $\text{cm}^{-1}$

M.P. = 167  $^{\circ}\text{C}$

HPLC : 99.0 %

25 **Example 96 : 3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

To a round bottom flask protected from the moisture are added successively 0.220 g (0.5 mmol) of the compound of Example 95 in 5 ml of  $\text{CH}_3\text{CN}$ , and under stirring 0.150 g (5



- mmol) of powder of paraformaldehyd, 0.095 g (1.5 mmol) of  $\text{NaBH}_3\text{CN}$  and 100  $\mu\text{l}$  of acetic acid. After 2 hours at room temperature and 1h30 under reflux, the reaction mixture is taken up in dichloromethane and washed with a solution of  $\text{NaOH}$  1M. The organic phase is decanted, washed, dried and then concentrated under vacuum. The product is
- 5 recrystallized from acetonitrile to provide 0.130 g (yield : 55%) of the desired compound.  
TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.42  
NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 2.80 (s,6H); 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.00 (s,2H); 6.60 (d,2H); 6.90 (d,2H); 7.15-7.25 (m,4H); 7.50 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.2 (t,1H).
- 10 IR : 1699, 1654, 1640, 1616, 1508, 1324, 1324  $\text{cm}^{-1}$   
M.P. = 205.0°C  
HPLC : 98.9 %

**Example 97 : 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

- 15 To a round bottom protected from the moisture is added 0.190 g (0.43 mmol) of the compound of Example 95 in 10 ml of dichloromethane. The solution is stirred and 36  $\mu\text{l}$  (40 mg, 0.51 mmol) of acetyl chloride and 72  $\mu\text{l}$  of triethylamine are added. After 1 hour at room temperature 36  $\mu\text{l}$  of acetyl chloride and 72  $\mu\text{l}$  of triethylamine are added. After 1 hour, the organic phase is washed with a solution of  $\text{HCl}$  1M and dried. A chromatography
- 20 over silica gel (dichloromethane/ether) provides 0.120 g (yield: 57%) of the desired product.  
TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.17  
NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.0 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.05 (s,2H); 6.90 (d,2H); 7.20-7.30 (m,4H); 7.45 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2
- 25 (t,1H); 9.85 (s,1H).  
IR : 3330, 1661, 1617, 1511, 1475, 1322, 1244, 825, 752  $\text{cm}^{-1}$   
M.P. = 251.0 °C  
HPLC : 100.0 %

**Example 98 : 3-[4-(N,N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and methanesulfonyl chloride.

5 TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.40

NMR: DMSO <sup>1</sup>H δ (ppm): 3.50 (s,6H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.40-7.50 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 1655, 1639, 1507, 1376, 1252, 1157, 905, 761 cm<sup>-1</sup>

10 M.P. = 198 °C

HPLC : 100.0 %

**Example 99 : 3-(Benzofurazan-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using  
15 the compound obtained in the Step 1 of the Example 34 and 5-bromomethyl benzofurazan.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.80

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.60 (m,2H); 7.90 (s,1H); 8.0 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 2370, 1701, 1653, 1617, 1499, 1477, 1326, 1243, 1181, 1028, 881, 781 cm<sup>-1</sup>

20 M.P. = 140.5°C

HPLC : 100.0 %

**Example 100 : 3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using  
25 the compound obtained in the Step 1 of the Example 34 and 4-fluorophenoxyethyl bromide.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.20 (d,2H); 4.3-4.4 (m,2H); 4.4-4.50 (m,2H); 6.80-7.0 (m,4H); 7.0-7.1 (m,2H); 7.2-7.30 (m,2H); 7.4-7.5 (m,1H); 8.20-8.30 (m,1H); 8.60-8.70 (m,1H); 9.2 (t,1H).

IR : 1707, 1656, 1641, 1520, 1475, 1247, 1209, 1034, 828, 752  $\text{cm}^{-1}$

5 M.P. = 159.6  $^{\circ}\text{C}$

HPLC : 99.7 %

**Example 101 : 3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 2-chloroethyl phenyl sulphone.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.55

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (s,3H); 3.6-3.70 (m,2H); 3.75 (s,3H); 4.3 (d,2H); 4.4-4.50 (m,2H); 6.90 (d,2H); 7.30 (d,2H); 7.4-7.7 (m,4H); 7.9 (d,2H); 8.20 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3274, 1708, 1663, 1638, 1514, 1499, 1249, 1147, 1034, 825, 746  $\text{cm}^{-1}$

M.P. = 192.9 $^{\circ}\text{C}$

HPLC : 96.0 %

20 **Example 102 : 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 4-chloromethyl-2-fluoro-1-methoxy-benzene.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

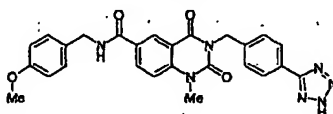
25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.75 (s,3H); 3.80 (s,3H); 4.4 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.20 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 3411, 2362, 1705, 1644, 1617, 1513, 1325, 1275, 1246, 1028, 827, 786  $\text{cm}^{-1}$

M.P. = 136 °C

HPLC : 100.0 %

**Example 103: 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



5

A solution of 3 g (6.6 mmol) of compound of the Example 60 in 100 ml of toluene, 1.3 g (19.8 mmol) of  $\text{NaN}_3$  and 2.72 g (19.8 mmol) of triethylamine hydrochloride are heated at 80°C under an inert atmosphere. After 5 hours, 10 ml of DMF are added and the reflux is maintained overnight. After cooling, the precipitate is filtered and washed successively with AcOEt, MeOH and HCl 3N. The solid obtained is treated under reflux by a mixture of AcOEt/MeOH and filtered. A chromatography over silica gel (DMF with  $\text{NH}_4\text{OH}$  10%) provides 1.2 g of the desired compound (yield : 36%).

10

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 80/20  $R_f$  = 0.30

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (bs, 1H); 3.55 (s, 3H); 3.70 (s, 3H); 4.4 (m, 2H); 5.20 (s, 2H); 6.90 (m, 2H); 7.25 (m, 2H); 7.50 (m, 3H); 8.0 (m, 2H); 8.3 (m, 1H); 8.70 (s, 1H); 9.2 (m, 1H).

15

M.P. = 286°C

HPLC : 96.7 %

**Example 104 : 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 3-(4-chloromethyl-phenyl)-5-methyl-[1,2,4]oxadiazole (which is obtained in 4 steps from 4-hydroxymethyl-benzonitrile).

20

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.50

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 2.60 (s, 3H); 3.60 (s, 3H); 3.80 (s, 3H); 4.55 (m, 2H); 5.25 (s, 2H); 6.60 (s, 1H); 6.85 (m, 2H); 7.30 (m, 3H); 7.55 (m, 2H); 7.90 (m, 2H); 8.3 (m, 1H); 8.50 (s, 1H).

25

M.P. = 235.0°C

HPLC : 95.1 %

**Example 105 : 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

To a round bottom containing 4Å molecular sieves, 5 ml of DMF, 76 mg (1.02 mmol) of *N*-hydroxy-acetamidine and 25 mg (1.02 mmol) of NaH are introduced. The mixture is stirred for 15 minutes and 0.5 g (1.02 mmol) of compound of the Example 34 is added. The reaction is heated at 65°C for 4 hours and then filtered over Celite. The filtrate is poured onto 100 ml of water. The precipitate obtained is filtered, washed successively by ethanol, water and ether, and dried to provide 0.210 g (yield: 40%) of the desired compound.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.50

NMR: DMSO <sup>1</sup>H δ (ppm): 3.3 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (m,2H); 5.25 (s,2H); 6.90 (m,2H); 7.25 (m,2H); 7.55 (m,3H); 8.0 (d,2H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H).

M.P. = 226.0°C

HPLC : 98.6 %

**Example 106 : Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 2-chloro-4-chloromethyl-benzoate.

NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (m,2H); 7.25 (m,3H); 7.60 (d,1H); 7.75 (d,1H); 7.95 (s,1H); 8.3 (m,1H); 8.70 (s,1H); 9.2 (m,1H).

M.P. = 229.0°C

HPLC: 98.8 %

**Example 107 : 2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained by hydrolysis of the compound of Example 106 with a solution of aqueous methanol and  $K_2CO_3$ .

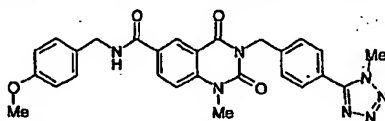
TLC :  $CH_2Cl_2$  / MeOH 90/10  $R_f$  = 0.30

NMR: DMSO  $^1H$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (m,2H); 5.20 (s,2H); 6.85 (m,2H); 7.20 (m,3H); 7.60 (m,1H); 7.70 (m,1H); 7.95 (m,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 13.2 (s,1H).

M.P. = 216.0°C

HPLC: 96.5 %

**Example 108 : 1-Methyl-3-[4-(1-methyl-1H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-1-methyl-1H-tetrazole

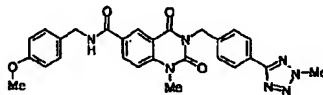
TLC :  $CH_2Cl_2$  / MeOH 90/10  $R_f$  = 0.40

NMR: DMSO  $^1H$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.10 (s,3H); 4.40 (m,2H); 5.20 (s,2H); 6.80 (d,2H); 7.25 (d,2H); 7.50 (m,3H); 7.80 (m,2H); 8.2 (d,1H); 8.60 (s,1H); 9.2 (s,1H).

M.P. = 143.0°C

HPLC : 100 %

**Example 109 : 1-Methyl-3-[4-(2-methyl-2H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-2-methyl-2H-tetrazole.

TLC :  $CH_2Cl_2$  / MeOH 90/10  $R_f$  = 0.50

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.40 (m,5H); 5.20 (s,2H); 6.90 (m,2H); 7.25 (m,2H); 7.50 (m,3H); 8.0 (m,2H); 8.3 (d,1H); 8.60 (s,1H); 9.2 (m,1H).

M.P. = 226.0°C

HPLC : 98.2 %

5     **Example 110 :Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methoxy-benzoate.

10     TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10 Rf = 0.60

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.80 (s,3H); 3.85 (s,3H); 3.90 (s,3H); 4.55 (d,2H); 5.20 (s,2H); 6.45 (m,1H); 6.80 (d,2H); 7.05 (d,1H); 7.20 (m,4H); 7.70 (d,1H); 8.3 (d,1H); 8.50 (s,1H).

M.P. = 170.0°C

15     HPLC : 98.6 %

**Example 111 :2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

20     The compound is obtained by hydrolysis of compound of the Example 110 using as reagent  $\text{K}_2\text{CO}_3$  in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10 Rf = 0.50

25     NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (s,2H); 5.15 (s,2H); 6.90 (m,3H); 7.10 (s,1H); 7.30 (m,2H); 7.60 (m,2H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 12.5 (bs,1H).

M.P. = 189°C

HPLC: 100.0 %

**Example 112 :Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

To a stirred solution of 1 g (1.93 mmol) of compound of the Example 111 in 15 ml of dichloromethane, maintained at 0°C, are added dropwise, under an inert atmosphere, 7.7 ml (7.7 mmol) of BCl<sub>3</sub> 1M/l in dichloromethane. After 15 minutes of stirring at 0°C and 1 hour at room temperature, the reaction mixture is poured on ice and extracted by ethyl acetate. The organic phase is dried and concentrated under vacuum. The precipitate obtained is purified by chromatography over silica gel (dichloromethane/methanol: 99/1) to provide 0.460 g (yield : 47%) of the desired product.

**TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

**NMR:** DMSO <sup>1</sup>H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 3.85 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.85 (m,4H); 7.25 (d,2H); 7.55 (d,1H); 7.70 (d,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 10.5 (s,1H).

**M.P.** = 205.0 °C

**HPLC :** 100.0 %

**Example 113 :2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K<sub>2</sub>CO<sub>3</sub> in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

**TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

**NMR:** DMSO <sup>1</sup>H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.80 (m,4H); 7.25 (m,2H); 7.55 (m,1H); 7.70 (d,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 11.3 (bs,1H); 13.8 (s,1H).

**M.P.** = 262.0 °C

**HPLC :** 98.2 %

**Example 114 :Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methyl benzoate.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.80

5 NMR: DMSO <sup>1</sup>H δ (ppm): 2.5 (s,3H); 3.50 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (s,2H); 5.10 (s,2H); 6.90 (m,2H); 7.25 (m,4H); 7.50 (d,1H); 7.70 (d,1H); 8.2 (m,1H); 8.60 (s,1H); 9.2 (s,1H).

M.P. = 167.0°C

HPLC : 100.0 %

10 **Example 115 : 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained by hydrolysis of compound of the Example 114 using first as reagent K<sub>2</sub>CO<sub>3</sub> in a mixture of methanol and water, and secondly LiOH in reflux for 2 days. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired compound.

15 TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

NMR: DMSO <sup>1</sup>H δ (ppm): 2.5 (s,3H); 3.55 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.80 (d,2H); 7.25-7.1 (m,4H); 7.55 (m,1H); 7.75 (m,1H); 8.2 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 12.7 (s,1H)

20 M.P. = 179.0 °C

HPLC : 95.6 %

**Example 116 : 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide**

25 **Step 1 : Methyl 2,4-dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of the Step 4 of Example 15 using the compound obtained in the Step 2 of the Example 20.

**Step 2: 2,4-Dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1.

5      **Step 3: 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide**

To a stirred solution of 0.2 g (0.65 mmol) of compound obtained in the preceding Step 2 in 7 ml of dichloromethane are added 0.113 g (0.65 mmol) of EDCI, 0.080 g (0.65 mmol) of HOBT and 0.064 g (0.060 ml, 0.65 mmol) of 3,4-methylenedioxy-benzylamine. After 20  
10 hours of stirring at room temperature and an usual treatment, 0.140 g (yield: 48%) of the desired product are obtained.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.80

NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.0 (s,2H); 6.80-6.95 (m,3H); 7.25-7.35 (m,2H); 7.55-7.60 (m,1H); 8.25-8.35 (m,1H); 8.45-8.50 (m,2H); 8.65  
15 (s,1H); 9.20 (t,1H).

IR : 3265, 1707, 1663, 1618, 1501, 1490, 1254, 1037, 925 cm<sup>-1</sup>

M.P. = 161.7°C

HPLC : 94.6 %

20      **Example 117 : 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Step 2 of the Example 116 and 4-methoxy-benzylamine. 0.280 g (yield : 25%) of the desired product is isolated after a chromatography over silica gel.

25      TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.80 (d,2H); 7.2-7.3 (m,4H); 7.55-7.60 (m,1H); 8.25-8.30 (m,1H); 8.45 (d,2H); 8.60 (s,1H); 9.20 (m,1H).

IR : 3231, 1706, 1657, 1625, 1505, 1324, 1248, 1039, 827  $\text{cm}^{-1}$

M.P. = 180.7 °C

HPLC : 94.3 %

**Example 118 : 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide**

To a stirred solution of 0.280 g (0.67 mmol) of compound of the Example 117 in 20 ml of dichloromethane, maintained at 0°C, are added, under an inert atmosphere, 1.7 g (0.63 ml, 6.7 mmol) of  $\text{BBr}_3$  in 2 ml of dichloromethane. After 20 minutes of stirring at room temperature, the reaction mixture is poured on a saturated solution of  $\text{NaHCO}_3$ , decanted, and extracted. The organic phase is dried and concentrated under vacuum to provide 0.150 g (yield : 53.4%) of the desired product.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.60

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.70 (d,2H); 7.15 (d,2H); 7.3 (d,2H); 7.55-7.60 (m,1H); 8.30 (d,1H); 8.50 (d,2H); 8.65 (s,1H); 9.20 (m,1H); 9.30 (s,1H)

IR : 3388, 1701, 1656, 1639, 1615, 1508, 1251, 830, 772, 751  $\text{cm}^{-1}$

M.P. = 137.7°C

HPLC : 91.1 %

**Example 119 : Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

**Step 1 : Benzyl 3-(4-methoxycarbonyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of Step 1-5 to Step 2-5 of the Preparation B using, in Step 1-5, 4-amino-isophthalic acid 1-benzylester 3-methyl ester and methyl 4-aminomethyl benzoate. The desired product is purified by reflux in methanol.

TC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.65

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.8 (s, 3H); 5.10 (s,2H); 5.35 (s,2H); 7.20-7.80 (m,8H); 7.80-7.90 (m,2H); 8.20-8.30 (m,1H); 8.50 (s,1H); 11.90 (s,1H).

HPLC : 97.0 %

**Step 2 : Benzyl 3-(4-methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the preceding Step 1.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.65

NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 3.80 (s,3H); 5.20 (s,2H); 5.35 (s,2H); 7.30-7.60 (m,8H); 7.80-7.90 (m,2H); 8.20-8.30 (m,1H); 8.60 (s,1H).

HPLC : 97.0 %

**Step 3 : 3-(4-Methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid**

To a stirred solution of 10.8 g (23.6 mmol) of the compound obtained in the preceding Step 2 in 120 ml of dichloromethane and 80 ml of methanol, are added 3.2 g of Pd/C at 10%. The reaction mixture is stirred under hydrogen atmosphere for 1 hour at room temperature, followed by filtration over Celite. The filtrate is concentrated under vacuum to give a first crystallized crop. The insoluble part is extracted three times by a mixture of methanol/water/saturated solution of NaHCO<sub>3</sub>. The organic phases are gathered and acidified to pH 1 by a concentrated solution of chlorhydric acid, to give to a second crop corresponding to the desired product. The two crops are put together and dried under vacuum to provide 6.9 g of the desired product (yield : 79%).

NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 3.80 (s,3H); 5.20 (s,2H); 7.40 (dd,2H); 7.60 (dd,1H); 7.90 (dd,2H); 8.30 (dd,1H); 8.60 (s,1H); 13.20 (bs,1H).

HPLC : > 97.0 %

**Step 4 : Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 3-methoxy-benzylamine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.80 (d,1H); 6.90 (m,2H); 7.25 (m,1H); 7.45 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H).

IR : 3435, 2361, 1716, 1703, 1666, 1617, 1498, 1455, 1282, 1125, 839, 749,  $\text{cm}^{-1}$

5 M.P. = 199.0°C

HPLC : 98.6 %

**Example 120 : 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

10 The compound is obtained by hydrolysis of compound of the Example 119 using as reagent  $\text{K}_2\text{CO}_3$  in a mixture of methanol and water under reflux for 8 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.40

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.80 (d,1H); 6.90 (m,2H); 7.25 (t,1H); 7.45 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H); 12.85 (bs,1H)

IR : 3395, 2345, 1719, 1647, 1616, 1501, 1310, 1238, 1052, 839, 781, 751  $\text{cm}^{-1}$

M.P. = 279.0°C

HPLC : 97.4 %

20 **Example 121 : Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-methylthio-benzylamine.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.45 (s,3H); 3.55 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.20 (m,4H); 7.45 (d,2H); 7.55 (s,1H); 7.90 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3395, 1708, 1656, 1641, 1508, 1479, 1330, 1280, 1254, 1117, 783, 749,  $\text{cm}^{-1}$

M.P. = 172 °C

HPLC : 99.2 %

**Example 122 : 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

- 5 The compound is obtained by hydrolysis of compound of the Example 121 using as reagent  $K_2CO_3$  in a mixture of methanol and water under reflux for 48 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC :  $CH_2Cl_2$  / MeOH 90/10  $R_f$  = 0.35

- 10 NMR: DMSO  $^1H$   $\delta$  (ppm): 2.45 (s,3H); 3.55 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.25 (m,4H); 7.40 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H); 12.85 (bs,1H);  
IR : 1705, 1656, 1642, 1616, 1479, 1330, 1247, 1101, 1020, 760, 751  $cm^{-1}$

M.P. = 171 °C

HPLC : 98.0 %

- 15 **Example 123 : Methyl 4-[1-methyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-trifluoromethoxy-benzylamine.

- 20 TLC :  $CH_2Cl_2$  / MeOH 95/5  $R_f$  = 0.35

NMR: DMSO  $^1H$   $\delta$  (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.50 (d,2H); 5.20 (s,2H); 7.30 (d,2H); 7.35-7.50 (m,4H); 7.55 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.30 (t,1H).

IR : 1712, 1656, 1639, 1506, 1274, 1156, 1104, 751  $cm^{-1}$

M.P. = 212 °C

- 25 HPLC : 99.6 %

**Example 124 : Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 4-fluorobenzylamine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.45

5 NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.10-7.20 (m,2H); 7.30-7.40 (m,2H); 7.40-7.50 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H).

IR : 1709, 1657, 1618, 1499, 1264, 768, 749, 716 cm<sup>-1</sup>

M.P. = 198 °C

HPLC : 98.2 %

10 **Example 125 : 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 124.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.25

15 NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.10-7.20 (m,2H); 7.30-7.40 (m,2H); 7.45 (d,2H); 7.55 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H); 12.90 (bs,1H)

IR : 3661, 2765, 1710, 1649, 1617, 1505, 1224, 829, 752 cm<sup>-1</sup>

M.P. = 272 °C

20 HPLC : 98.0 %

**Example 126 : Methyl 4-{6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate**

25 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and C-benzofurazan-5-yl-methylamine, which is obtained from 5-bromomethyl-benzofurazan by reaction in a first step with sodium diformylamide in acetonitrile at 70°C overnight, and in a second step by a treatment for 2 hours under reflux to a solution of ethanol/HCl 5%.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.70

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.85 (s,3H); 4.65 (d,2H); 5.25 (s,2H); 7.45 (d,2H); 7.60 (d,2H); 7.90 (m,3H); 8.00 (d,1H); 8.30 (d,1H); 8.65 (s,1H); 9.40 (t,1H).

IR : 3257, 1731, 1702, 1659, 1619, 1506, 1419, 1281, 1109, 877, 769, 751  $\text{cm}^{-1}$

M.P. = 234  $^{\circ}\text{C}$

5 HPLC : 98.6 %

**Example 127: 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 126. After acidification, the precipitate is  
10 filtered off.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.35

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.60 (d,2H); 5.20 (s,2H); 7.40 (d,2H); 7.60 (d,2H); 7.85 (d,3H); 8.00 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.40 (t,1H); 12.9 (bs,1H).

IR : 3249, 1708, 1662, 1617, 1479, 1427, 1322, 1250, 1008, 879, 790, 754  $\text{cm}^{-1}$

15 M.P. = 276  $^{\circ}\text{C}$

HPLC : 97.6 %

**Example 128 :Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**  
20

**Step 1 : 4-Amino-isophthalic acid 3-methyl ester**

The compound is obtained according to the procedure of the Step 3 of the Example 119 using as substrate 4-amino-isophthalic acid 1-benzylester 3-methyl ester.

**Step 2: 6-Amino-N-(4-methoxy-benzyl)-isophthalamic acid methyl ester**

25 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxy-benzylamine.

**Step 3 : Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-**



**quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 1-5 to 2-5 of the Preparation B using in the Step 1-5 the compound obtained in the preceding Step 2 and methyl 4-aminomethyl benzoate.

5 **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.55

**NMR**: DMSO <sup>1</sup>H δ (ppm): 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.20 (m,3H); 7.45 (d,2H); 7.90 (d,2H); 8.15 (d,1H); 8.50 (s,1H); 9.15 (t,1H); 11.8 (s,1H).

**IR** : 3265, 2935, 2553, 1719, 1665, 1637, 1514, 1459, 1275, 1105, 827, 751 cm<sup>-1</sup>

**M.P.** = 287.5 °C

10 **HPLC** : 98.3 %

**Example 129 :Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained the Example 128 and iodomethane in DMF with K<sub>2</sub>CO<sub>3</sub>. The  
15 desired compound crystallizes in a mixture of dichloromethane/ether.

**TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.55

**NMR**: DMSO <sup>1</sup>H δ (ppm): 1.25 (t,3H); 3.75 (s,3H); 3.85 (s,3H); 4.20 (d,2H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.60 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

20 **IR** : 3403, 2361, 1708, 1659, 1646, 1615, 1508, 1273, 1251, 1113, 847, 758 cm<sup>-1</sup>

**M.P.** = 190 °C

**HPLC** : 96.9 %

**Example 130 :4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

25 The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K<sub>2</sub>CO<sub>3</sub> in a mixture of methanol and water under reflux for 3 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.45

NMR: DMSO <sup>1</sup>H δ (ppm): 1.25 (t,3H); 3.70 (s,3H); 4.20 (q,2H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 12.85 (bs,1H)

5 IR : 2361, 1708, 1655, 1616, 1501, 1466, 1322, 1250, 1177, 1032, 823, 754 cm<sup>-1</sup>

M.P. = 160 °C

HPLC : 98.2 %

**Example 131 : 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

10 **Step 1 : Methyl 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the Step 1 of example 16.

15 **Step 2: 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1.

**Step 3: 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

20 The compound is obtained (0.160 g, yield : 63%) according to the procedure of the Step 3 of the Example 116 using the compound obtained in the preceding Step 2 and 4-(aminomethyl)pyridine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

25 NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.5 (d,2H); 5.10 (s,2H); 6.80-6.90 (m,2H); 7.30-7.35 (m,4H); 7.55-7.60 (m,1H); 8.25-8.30 (m,1H); 8.38-8.42 (m,2H); 8.70 (s,1H); 9.35 (t,1H).

IR : 3269, 1705, 1659, 1644, 1615, 1510, 1245, 1180, 842, 785 cm<sup>-1</sup>

M.P. = 213.9 °C

HPLC : 97.8 %

**Exemple 132 : 3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

To a stirred solution of 0.630 g (1.46 mmol) of compound of the Example 131 in 50 ml of dichloromethane are added, under an inert atmosphere, 3.7 g (1.3 ml, 14.6 mmol) of BBr<sub>3</sub> in 5 ml of dichloromethane. After 1 hour of stirring at room temperature, the reaction mixture is cooled and poured on 100 ml of a saturated solution of NaHCO<sub>3</sub>. The precipitate obtained is purified by chromatography over silica gel (gradient of methanol in dichloromethane) and solidified in dichloromethane to provide the desired compound.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

NMR: DMSO <sup>1</sup>H δ (ppm): 3.45 (s,3H); 4.45 (d,2H); 5.0 (s,2H); 6.60 (d,2H); 7.1 (d,2H); 7.25 (d,2H); 7.5 (d,1H); 8.20 (d,1H); 8.40 (d,2H); 8.60 (s,1H); 9.20 (s,1H); 9.20 (t,1H).

IR : 3048, 1705, 1659, 1642, 1507, 1479, 1328, 1244, 831 cm<sup>-1</sup>

M.P. = 262.0 °C

HPLC : 94.8 %

**Example 133: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

The compound is obtained according to the procedure of the Example 33 using the same substrate and 4-picolylamine in the step of amidification.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.25

NMR: DMSO <sup>1</sup>H δ (ppm): 3.45 (s,3H); 4.5 (d,2H); 7.3 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.5 (d,2H); 8.6 (s,1H); 9.35 (t,1H); 11.7 (s,1H).

IR : 3185,1686,1618,1479,1417,1326,782 cm<sup>-1</sup>

M.P. = 292 °C

HPLC : 96.4 %

**Step 2: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and  $\alpha$ -bromo-*para*-toluonitrile.

5     **TLC :** AcOEt R<sub>f</sub> = 0.55

**NMR:** CDCl<sub>3</sub> <sup>1</sup>H  $\delta$  (ppm): 3.60 (s, 3H); 4.60 (d, 2H); 5.30 (s, 2H); 7.3 (m, 3H); 7.60 (s, 4H); 8.40 (m, 1H); 8.45 (m, 2H); 8.65 (m, 1H); 8.80 (s, 1H).

**M.P.** = 258°C

**HPLC :** 98.9 %

10     **Example 134 : 1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and 4-(3-chloro-propenyl)-pyridine hydrochloride.

15     **TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

**NMR:** DMSO <sup>1</sup>H  $\delta$  (ppm): 3.60 (s, 3H); 4.50 (m, 2H); 4.80 (m, 2H); 6.50 (m, 1H); 6.65 (m, 1H); 7.3 (m, 2H); 7.40 (m, 2H); 7.60 (d, 1H); 8.25 (d, 1H); 8.50 (m, 4H); 8.65 (s, 1H); 9.35 (m, 1H).

**M.P.** = 117°C

20     **HPLC :** 99.5 %

**Example 135 : Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl-4-(bromomethyl)-benzoate.

25

**TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.45

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.5 (d,2H); 5.20 (s,2H); 7.3 (m,2H); 7.45 (d,2H); 7.60 (d,1H); 7.90 (m,2H); 8.25 (d,1H); 8.5 (m,2H); 8.65 (s,1H); 9.35 (t,1H).

IR : 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751  $\text{cm}^{-1}$

M.P. = 236 °C

5 HPLC : 97.5 %

**Example 136 : 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 135. The corresponding hydrochloride is  
10 obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 2.4-4.40 (m,1H); 3.60 (s,3H); 4.15 (t,2H); 5.20 (s,2H); 7.40 (d,2H); 7.60 (d,1H); 7.90 (m,4H); 8.30 (d,1H); 8.70 (s,1H); 8.80 (d,1H); 9.65 (t,1H); 12.9 (bs,1H).

15 IR : 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751  $\text{cm}^{-1}$

M.P. = 268 °C

HPLC : 97.9 %

**Example 137 : Methyl (4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetate**

20 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl 4-(bromomethyl-phenyl) acetate.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.45

25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50-3.60 (s,6H); 3.65 (s,2H); 4.5 (t,2H); 5.15 (s,2H); 7.20 (m,2H); 7.20-7.35 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.5 (d,2H); 8.65 (s,1H); 9.35 (t,1H).

IR : 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751  $\text{cm}^{-1}$

M.P. = 141 °C

HPLC : 96.4 %

**Example 138 : (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetic acid**

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 137. The corresponding hydrochloride is obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 2.50-5.50 (bs, HCl+OH); 3.45-3.60 (2s, 5H); 4.70 (d, 2H); 5.15 (s, 2H); 7.15 (d, 2H); 7.25 (d, 2H); 7.55 (d, 1H); 7.85 (d, 2H); 8.30 (d, 1H); 8.65 (s, 1H); 8.75 (d, 2H); 9.55 (t, 1H).

IR : 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751  $\text{cm}^{-1}$

M.P. = 241  $^{\circ}\text{C}$

HPLC : 97.5 %

**Example 139 : Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate**

To a stirred suspension of 0.500 g (1.10 mmol) of compound of the Example 135 in 20 ml of dichloromethane, maintained at  $-20^{\circ}\text{C}$ , are added 0.250 g (1.10 mmol) of *meta*-chloroperbenzoic acid in 5 ml of dichloromethane. After stirring overnight at room temperature, the reaction mixture is washed successively with a saturated solution of  $\text{Na}_2\text{CO}_3$  and water. The organic phase is dried and concentrated under vacuum. A chromatography over silica gel (gradient of methanol in dichloromethane) followed by a solidification in dichloromethane/ether provides 0.300 g (yield : 57%) of the desired product.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.28

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s, 3H); 3.85 (s, 3H); 4.45 (d, 2H); 5.25 (s, 2H); 7.3 (d, 2H); 7.45 (d, 2H); 7.60 (d, 1H); 7.90 (d, 2H); 8.15 (d, 2H); 8.30 (s, 1H); 8.65 (s, 1H); 9.35 (t, 1H).

IR : 1705, 1655, 1617, 1478, 1283, 750, 711  $\text{cm}^{-1}$

M.P. = 218  $^{\circ}\text{C}$

HPLC : 99.1 %

**Example 140 : 4-{1-Methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 139.

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.55 (d,2H); 5.20 (s,2H); 7.30-7.50 (m,4H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.35 (t,1H); 12.9 (bs,1H).

IR : 1702, 1655, 1617, 1479, 1245, 753  $\text{cm}^{-1}$

M.P. = 192  $^{\circ}\text{C}$

HPLC : 98.4 %

**Example 141 : Methyl{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-1-yl}-acetate**

The compound is obtained by alkylation of the compound of Example 3 using  $\text{K}_2\text{CO}_3$  and methylbromoacetate in DMF.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.70

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.70 (s,3H); 4.40 (d,2H); 5.05 (s,2H); 5.15 (s,2H); 6.0 (s,2H); 6.85 (m,3H); 7.30 (m,5H); 7.55 (d,1H); 8.20 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3282, 2361, 1736, 1669, 1632, 1464, 1370, 1236, 1040, 833, 776, 758  $\text{cm}^{-1}$

M.P. = 194.0  $^{\circ}\text{C}$

HPLC : 97.6 %

**Example 142 : {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl}-acetic acid**

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 141.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.70

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 4.35 (d,2H); 4.90 (s,2H); 5.15 (s,2H); 5.95 (s,2H); 6.80 (m,3H); 7.30 (m,5H); 7.50 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.20 (t,1H); 13.25 (bs,1H).

IR : 3346, 2935, 1709, 1668, 1612, 1499, 1467, 1305, 1250, 1117, 1036, 873  $\text{cm}^{-1}$

M.P. = 163.0  $^{\circ}\text{C}$

5 HPLC : 99.6 %

**Example 143 :Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 using the compound obtained in the Example 37 and methyl 4-(bromomethyl)-benzoate.

10 TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.90 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.0 (s,2H); 6.80-6.95 (m,3H); 7.45 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3418, 1713, 1666, 1657, 1617, 1497, 1477, 1280, 1252, 1038, 770, 749  $\text{cm}^{-1}$

15 M.P. = 233.5  $^{\circ}\text{C}$

HPLC : 99.6 %

**Example 144 :4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid**

20 The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 143.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.40

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 5.95 (s,2H); 6.80-6.95 (m,3H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.30 (d,1H); 8.60 (s,1H); 9.20 (t,1H); 12.85 (s,1H).

25 IR : 3377, 3233, 1717, 1698, 1665, 1649, 1502, 1481, 1236, 751  $\text{cm}^{-1}$

M.P. = 295.7  $^{\circ}\text{C}$

HPLC : 97.9 %



**Example 145: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-sulfamoyl-benzylamide**

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C and 4-(aminomethyl)benzene sulfonamide hydrochloride hydrate.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.37

NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2- 7.35 (m,7H); 7.50 (d,2H); 7.60 (d,1H); 7.80 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.35 (t,1H)

IR : 3290, 1709, 1652, 1618, 1503, 1321, 1154, 702 cm<sup>-1</sup>

M.P. = 266 °C

HPLC : 97.5 %

**Example 146 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid [3-(pyridin-4-ylsulfanyl)-propyl]-amide**

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 3-(pyridin-4-ylsulfanyl)-propylamine and dichloromethane as solvent. (The reactant 3-(pyridin-4-ylsulfanyl)-propylamine is obtained according to the method described in *Bioorg. Med. Chem.*, 1996, 4, 557-562).

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

NMR: DMSO <sup>1</sup>H δ (ppm): 1.8-1.90 (m,2H); 3.1-3.20 (m,2H); 3.4-3.50 (m,2H); 3.60 (s,3H); 5.20 (s,2H); 7.2- 7.40 (m,7H); 7.50-7.55 (m,1H); 8.20 (d,1H); 8.30-8.40 (m,2H); 8.60(s,1H); 8.80 (t,1H).

IR : 3308, 1705, 1662, 1636, 1578, 1509, 1447, 1321, 804, 712 cm<sup>-1</sup>

M.P. = 130.7 °C

HPLC : 99.2 %

**Example 147: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (4-morpholin-4-yl-butyl)-amide**

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Preparation C, 4-morpholin-4-yl-butylamine, and dichloromethane as solvent. (The reactant 4-morpholin-4-yl-butylamine is obtained according to the method described in *J. Med. Chem.*, 1997, 40, 3915-3925).

5     TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

NMR: DMSO <sup>1</sup>H δ (ppm): 1.4-1.60 (m,4H); 2.2-2.35 (m,6H); 3.20-3.35 (m,2H); 3.55 (s,3H); 3.5-3.60 (m,4H); 5.20 (s,2H); 7.2-7.35 (m,5H); 7.50 (d,1H); 8.20-8.25 (m,1H); 8.60 (s,1H); 8.70 (t,1H)

IR : 3402, 2942, 1707, 1645, 1476, 1327, 1118, 763 cm<sup>-1</sup>

10    M.P. = 170.6 °C

HPLC : 99.3 %

**Example 148 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-benzyl-piperidin-4-yl)-amide**

15    The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 4-amino-1-benzylpiperidine, and dichloromethane as solvent. The desired compound crystallizes from a mixture of dichloromethane and ether.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

20    NMR: DMSO <sup>1</sup>H δ (ppm): 1.60 (m,2H); 1.75 (m,2H); 2.0 (t,2H); 2.8 (d,2H); 3.45 (s,2H); 3.55 (s,3H); 3.75 (m,1H); 5.15 (s,2H); 7.30 (m,10H); 7.55 (d,1H); 8.20 (d,1H); 8.50 (d,1H); 8.60 (s,1H).

IR : 3257, 2943, 2749, 1709, 1656, 1633, 1511, 1332, 1242, 1077, 829, 750 cm<sup>-1</sup>

M.P. = 219.4 °C

HPLC : 98.6 %

25    **Example 149 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide**

To a round bottom protected from moisture and under inert atmosphere are introduced 1.9 g (4.4 mmol) of compound of Example 13 in 200 ml of dichloromethane. To the stirred

solution are added dropwise 4.2 ml (11.1 g, 44 mmol) of  $\text{BBr}_3$  in 17 ml of dichloromethane. After 30 minutes at room temperature the reaction mixture is poured to a 500 ml saturated solution of  $\text{NaHCO}_3$ , extracted with dichloromethane, dried and concentrated under vacuum. A crystallization of the crude product in methanol/ether provides 1.35 g (yield : 74%) of the desired compound.

**TLC :**  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f = 0.55$

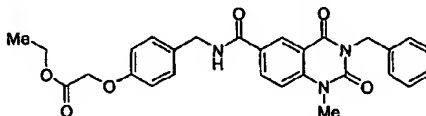
**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.7-6.75 (m,2H); 7.10-7.20 (m,2H); 7.2-7.40 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 9.0-9.3 (bs,1H).

**IR :** 3314, 1698, 1635, 1622, 1500, 1480, 1453, 1255, 826, 748  $\text{cm}^{-1}$

**M.P. =** 191.8  $^{\circ}\text{C}$

**HPLC :** 96.4 %

**Example 150 : Ethyl (4-[[[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl]-phenoxy)-acetate**



To a round bottom protected from moisture and under inert atmosphere are introduced 0.45 g (1.08 mmol) of compound of Example 149 in 13.5 ml of DMF. To the stirred solution are added 0.3 g of  $\text{K}_2\text{CO}_3$  (2.16 mmol) and 0.24 ml (2.016 mmol) of ethyl bromoacetate. After 1 hour at 60 $^{\circ}\text{C}$  the reaction mixture is concentrated under vacuum. The crude product is taken up in dichloromethane, washed with water, dried and concentrated under vacuum to provide 0.410 g (yield : 75.8%) of the desired compound.

**TLC :**  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f = 0.70$

**NMR:** DMSO  $^1\text{H}$   $\delta$  (ppm): 1.2 (t,3H); 3.60 (s,3H); 4.15 (q,2H); 4.45 (d,2H); 4.80 (s,2H); 5.20 (s,2H); 6.90 (d,2H); 7.2-7.40 (m,7H); 7.5 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

**IR :** 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750  $\text{cm}^{-1}$

**M.P. =** 172.6  $^{\circ}\text{C}$

**HPLC :** 97.8 %

**Example 151 : (4-[[[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-**

**carbonyl)-amino]-methyl}-phenoxy)-acetic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 150.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

5 NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 4.65 (s,2H); 5.15 (s,2H); 6.85 (d,2H); 7.2-7.40 (m,7H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 12.95 (bs,1H).

IR : 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750 cm<sup>-1</sup>

M.P. = 195.6 °C

HPLC : 98.3 %

10 **Example 152 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoylmethoxy-benzylamide**

The compound is obtained according to the procedure of the Example 1 using the compound of Example 151 and dimethylamine 2M in solution in THF.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70

15 NMR: DMSO <sup>1</sup>H δ (ppm): 2.80 (s,3H); 3.0 (s,3H); 3.55 (s,3H); 4.40 (d,2H); 4.80 (s,2H); 5.20 (s,2H); 6.90 (d,2H); 7.2-7.40 (m,7H); 7.50 (d,1H); 8.20 (d,1H); 8.65 (s,1H); 9.25 (t,1H).

IR : 3276, 1704, 1659, 1635, 1499, 1317, 1240, 1066, 750 cm<sup>-1</sup>

M.P. = 152.7 °C

20 HPLC : 96.5 %

**Example 153: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (3-phenyl-allyl)-amide**

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 3-phenyl-allylamine hydrochloride.

25 TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.80

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.10 (m,2H); 5.20 (s,2H); 6.35 (m,1H); 6.60 (m,1H); 7.20-7.35 (m,8H); 7.40 (m,2H); 7.55 (d,1H); 8.30 (d,1H); 8.70 (s,1H); 9.00 (m,1H).

M.P. = 193.0 °C

5 HPLC : 99.7 %

**Example 154 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-cyano-benzylamide**

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 4-amino-benzyl benzonitrile. The desired product is solidified in a mixture of dichloromethane/ether.

10 TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.46

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.60 (d,2H); 5.15 (s,2H); 7.20-7.40 (m,5H); 7.45-7.60 (m,3H); 7.80 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.40 (t,1H).

IR : 3305, 2224, 1708, 1664, 1638, 1507, 1318, 751  $\text{cm}^{-1}$

15 M.P. = 245.0 °C

HPLC : 96.2 %

**Example 155 : 4-[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-benzoic acid**

20 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 11.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.30

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.55 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.25 (m,5H); 7.40 (d,2H); 7.55 (d,1H); 7.90(d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.30 (t,1H); 12.90 (bs,1H).

25 IR : 3395, 1707, 1698, 1642, 1618, 1501, 1431, 1291, 1242, 938, 829, 759  $\text{cm}^{-1}$

M.P. = 228.5 °C

HPLC : 96.9 %

**Example 156 : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoyl-benzylamide**

The compound is obtained according to the procedure of the Example 1 using the compound of the Example 155 and dimethylamine in solution 2M in THF.

- 5     **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.70  
      **NMR**: DMSO <sup>1</sup>H δ (ppm): 3.0 (m,6H); 3.55 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.30 (m,9H); 7.60 (d,1H); 8.30 (d,1H); 8.65 (s,1H); 9.30 (t,1H).  
      **IR** : 3249, 2361, 1705, 1657, 1609, 1504, 1452, 1254, 1069, 1020, 839, 750 cm<sup>-1</sup>  
      **M.P.** = 194.7 °C  
10    **HPLC** : 96.8 %

**Example 157 : 3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the Step 1-5 to 3-5 of the preparation B using in the Step 1-5 4-dimethylamino-benzyl isocyanate, and then according to the procedure of

15    **Example 1** using the compound obtained in the preceding step and 4-methoxy-benzylamine

- NMR**: DMSO <sup>1</sup>H δ (ppm): 2.80 (s,6H); 3.70 (s,3H); 4.40 (d,2H); 4.95 (s,2H); 6.60 (d,2H); 6.85 (d,2H); 7.15-7.25 (m,5H); 8.10 (dd,1H); 8.50 (s,1H); 9.10 (t,1H); 11.7 (s,1H).  
      **IR** : 3177, 1729, 1630, 1512, 1445, 1249, 765 cm<sup>-1</sup>  
20    **M.P.** = 267 °C  
      **HPLC**: 98.5%

**Example 158 : 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

- 25    The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and 2.5 equivalents of methanesulfonyl chloride.  
      **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.22

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 2.90 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.10 (d,2H); 7.25 (d,2H); 7.30 (d,2H); 7.55 (s,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 9.70 (s,1H)

IR : 1655, 1615, 1513, 1500, 1325, 1248, 1148  $\text{cm}^{-1}$

5 M.P. = 224 °C

HPLC : 98.8 %

**Example 159: *tert*-Butyl {5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate**

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and *tert*-butyl (5-bromomethyl-pyridin-2-yl)-carbamate.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

15 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 1.45 (s,9H); 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 7.70 (m,2H); 8.25-8.30 (m,2H); 8.65 (s,1H); 9.2 (t,1H); 9.70 (s,1H)

IR : 1711, 1654, 1614, 1508, 1478, 1302, 1243, 1159  $\text{cm}^{-1}$

M.P. = 204 °C

HPLC : 99.3 %

20 **Example 160: 3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained by deprotection of compound of the Example 159 by using trifluoroacetic acid in dichloromethane.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.40

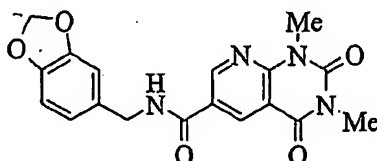
25 NMR: DMSO  $^1\text{H}$   $\delta$  (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 4.95 (s,2H); 5.80 (bs,2H); 6.35 (d,1H); 6.90 (d,2H); 7.25 (d,2H); 7.40 (dd,1H); 7.50 (d,1H); 7.95 (s,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.2 (t,1H)

IR : 1704, 1648, 1615, 1509, 1477, 1245  $\text{cm}^{-1}$

M.P. = 155 °C

HPLC : 99.5 %

**Example 161 : 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**



5           **Step 1 : 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.**

The compound is obtained by hydrolysis in a mixture of dioxan/water of ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylate (*Heterocycles* 1998, 48(12),2521-2528) in presence of LiOH.

10       TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.10

R.M.N.:DMSO <sup>1</sup>H δ (ppm): 3.30 (s,3H) ; 3.60 (s,3H) ; 8.70 (s,1H) ; 9.15 (s,1H) ; 13.5 (bs,1H)

**Step 2: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

15       The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.90

NMR.:DMSO <sup>1</sup>H δ (ppm) : 3.35 (s,3H); 3.6 (s,3H); 4.40 (d,2H); 6.0 (s,2H); 6.75-6.85 (m,2H); 6.90 (s,1H); 8.80 (s,1H); 9.15 (s,1H); 9.30 (t,1H).

20       IR : 3227, 1705, 1663, 1632, 1608, 1498, 1299, 1250, 1040, 794 cm<sup>-1</sup>

M.P. = 218.4°C

HPLC : 94.6 %

**Example 162: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**



**Step 1 : 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid**

The compound is obtained by hydrolysis in a mixture of dioxan/water of methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylate

5 (Heterocycles 1994, 37(1), 563-570) in presence of LiOH.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.01

NMR.:DMSO <sup>1</sup>H δ (ppm): 3.30 (s,3H); 3.60 (s,3H); 8.40 (s,1H); 9.00 (s,1H); 13.3 (bs,1H)

**Step 2: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

10 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.90

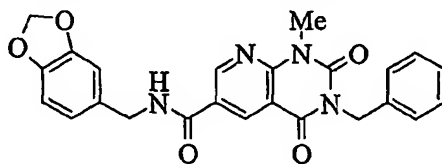
NMR.:DMSO <sup>1</sup>H δ (ppm): 3.35 (s,3H); 3.65 (s,3H); 4.45 (d,2H); 6.0 (s,2H); 6.80-6.90 (m,2H); 6.95 (s,1H); 8.50 (s,1H); 8.95 (s,1H); 9.25 (t,1H).

15 IR : 3379, 1713, 1662, 1478, 1253, 1238, 924, 750 cm<sup>-1</sup>

M.P. = 288.7°C

HPLC : 96.3 %

**Example 163: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**



20

**Step 1: N'-(1-Benzyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-N,N-dimethyl-formamidine**

0.56 g (2.5 mmol) of 6-amino-3-benzyl-1H-pyrimidine-2,4-dione (Tetrahedron Letters, 1991, 32(45), 6534-6540) in 20 ml of DMF are stirred under inert atmosphere. 1 ml (7.5

25 mmol) of N,N'-dimethylformamide dimethyl acetal is added to this solution and the mixture is heated to reflux for 20 minutes. After cooling and concentration under vacuum, the residue is taken up in dichloromethane, and the organic phase is washed with water,

dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under vacuum until a low volume. Then the crude product is precipitate by addition of ether. After filtration 0.680g (yield : 72.6%) of the desired compound is obtained.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.80

5 NMR.:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.0 (s,3H); 3.15 (s,3H); 3.30 (s,3H); 4.90 (s,2H); 5.20 (s,1H); 7.2-7.35 (m,5H) ; 8.10 (s,1H)

**Step 2: *N'*-(1-Benzyl-5-iodo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-*N,N*-dimethyl-formamidine**

To a stirred solution of 0.68 g (2.38 mmol) of the compound obtained in the preceding Step 1 in 24 ml of anhydrous dichloromethane is added 0.64 g (2.85 mmol) of N-iodosuccinimide. After 30 minutes of reflux, the reaction mixture is cooled and the organic phase is washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under vacuum. The crude product is precipitated in ether to obtain 0.680 g (yield: 69.3%) of the desired compound.

15 NMR.: $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.05 (s,3H) ; 3.15 (s,3H) ; 3.40 (s,3H) ; 5.20 (s,2H) ; 7.2-7.30 (m,3H) ; 7.5-7.55 (m,2H) ; 7.7 (s,1H).

M.P. = 186.3°C

**Step 3: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester**

To a stirred solution of 0.68 g (1.65 mmol) of the compound obtained in the preceding Step 2 in 45 ml of anhydrous DMF are added successively 18 mg  $\text{Pd}(\text{OAc})_2$ , 8 mg of CuI, 330 mg of  $\text{K}_2\text{CO}_3$ , and 0.22 ml of ethyl acrylate. After 30 minutes under reflux, the reaction mixture is concentrated under vacuum. The residue is taken up in dichloromethane. The organic phase is filtered, washed two times with water, dried over  $\text{Na}_2\text{SO}_4$  and then concentrated under vacuum. The crude product is purified by chromatography over silica gel (dichloromethane/methanol : 97/3) and then crystallized from ether to give 0.320 g (yield:57%) of the desired compound.

25 TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 97.5/2.5  $R_f$  = 0.50

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 1.40 (t,3H) ; 3.70 (s,3H) ; 4.40 (q,2H) ; 5.30 (s,2H) ; 7.2-7.30 (m,3H) ; 7.5-7.55 (m,2H) ; 9.0 (s,1H) ; 9.2 (s,1H)

**Step 4: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine  
-6-carboxylic acid**

5 The compound is obtained by hydrolysis, in a mixture of dioxan/water in presence of LiOH, of the compound obtained in the preceding Step 3.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 90 / 10  $R_f$  = 0.10

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H) ; 5.20 (s,2H) ; 7.2-7.40 (m,5H) ; 8.75 (s,1H) ; 9.2 (s,1H) ; 13.5 (bs,1H)

10 HPLC = 100%

**Step 5: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine  
-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 4 and piperonylamine.

15 TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.60

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.2 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.40 (m,5H); 8.85 (s,1H); 9.2 (s,1H); 9.25 (t,1H).

IR : 3271, 1709, 1665, 1630, 1614, 1488, 1248, 1042, 937, 795  $\text{cm}^{-1}$

M.P. = 174.9°C

20 HPLC : 97.5 %

**Example 164: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-  
2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-  
carboxylic acid**

25 A solution of 1.3 g (4.17 mmol) of the compound obtained in the Step 4 of Example 163 and 3.1 g (23 mmol) of  $\text{AlCl}_3$  in 44 ml of benzene is stirred 2 hours at room temperature. After addition of a mixture water/ice, the reaction mixture is extracted successively with

ethyl acetate and dichloromethane. The aqueous layer is acidified at pH 1 by addition of concentrated HCl. The precipitate obtained is filtered off and washed with 10 ml of methanol and 10 ml of dichloromethane to provide the desired compound (yield: 62.9%)

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (s, 3H); 8.60 (s, 1H); 9.10 (s, 1H); 11.9 (bs, 1H); 13.5 (bs, 1H)

HPLC = 100%

**Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 2 and 4-methoxybenzylamine.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.45

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.50 (s, 3H); 3.7 (s, 3H); 4.40 (d, 2H); 6.85-6.95 (m, 2H); 7.25-7.30 (m, 2H); 8.80 (s, 1H); 9.15 (s, 1H); 9.30 (t, 1H); 11.85 (bs, 1H)

HPLC = 92%

**Step 3: Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate. After concretization in ether 0.41 g (yield: 71.1%) of the desired compound is isolated.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.80

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s, 3H); 3.80 (s, 3H); 3.90 (s, 3H); 4.45 (d, 2H); 5.2 (s, 2H); 6.90 (dd, 2H); 7.30 (dd, 2H); 7.50 (dd, 2H); 7.90 (dd, 2H); 8.90 (s, 1H); 9.20 (s, 1H); 9.30 (t, 1H);

HPLC = 96.8%

**Step 4: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid**

The compound is obtained according to the procedure of Example 35 using the compound obtained in the preceding Step 3.

NMR.:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.90 (d,2H); 8.85 (s,1H); 9.20 (s,1H); 9.30 (t,1H); 12.90 (bs,1H)

IR : 3292, 1718, 1695, 1667, 1633, 1609, 1497, 1301, 1242, 797  $\text{cm}^{-1}$

5 M.P. = 229.5  $^{\circ}\text{C}$

HPLC : 93.6 %

**Example 165: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido**

**[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

10 The compound is obtained (0.11 g ; yield=68.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-(bromomethyl)benzonitrile.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.70

NMR.:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.30 (d,2H); 7.55 (d,2H); 7.80 (d,2H); 8.85 (s,1H); 9.20 (s,1H); 9.30 (t,1H)

15 IR : 3230, 2230, 1710, 1673, 1635, 1609, 1494, 1303, 1252, 794  $\text{cm}^{-1}$

M.P. = 197  $^{\circ}\text{C}$

HPLC : 97.2 %

**Example 166: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido**

**[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

20 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-fluorobenzyl bromide.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.70

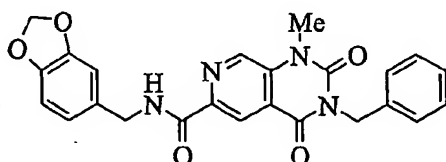
25 NMR.:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.8-6.90 (m,2H); 7.1-7.2 (m,2H); 7.25-7.35 (m,2H); 7.4-7.50 (m,2H); 8.85 (s,1H); 9.15 (s,1H); 9.30 (t,1H).

IR : 3260, 1709, 1664, 1616, 1497, 1245, 1221, 1035, 796  $\text{cm}^{-1}$

M.P. = 211.5  $^{\circ}\text{C}$

HPLC : 98.3 %

**Example 167: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**



**Step 1 : 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde**

5 A solution of 9.5 g (43.9 mmol) of 3-benzyl-6-methyl-1*H*-pyrimidine-2,4-dione (*Synthetic Communications* 1991, 2181-2188) and 129 ml of cold acetic acid are stirred 5 minutes, and 5.75 g of SeO<sub>2</sub> are added. The reaction mixture is heated to reflux for 2h30, filtered and concentrated under vacuum. The residue is taken up in dichloromethane. The unsoluble part is eliminated and the filtrate is concentrated under vacuum. A  
10 chromatography over silica gel (dichloromethane/methanol : 95/5) provides 4.0 g of the desired compound (yield:39.5%).

NMR:CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 5.20 (s,2H); 6.30 (s,1H); 7.2-7.30 (m,3H); 7.40-7.50 (m,2H); 9.0 (bs,1H); 9.60 (s,1H)

**Step 2: 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde dimethylhydrazone**

15 To a stirred solution of 3.6 g (15.6 mmol) of the compound obtained in the preceding Step 1 in 80 ml of anhydrous DMF are added 1.2 ml (0.94 g, 15.6 mmol) of dimethylhydrazine. After 1 hour of stirring at room temperature, the solvent is removed under vacuum and the residue is taken up in dichloromethane. The organic layer is washed, dried over Na<sub>2</sub>SO<sub>4</sub>  
20 and concentrated. A chromatography over silica gel (dichloromethane/methanol : 97/3) provides 2.5 g (yield:59%) of the desired compound.

NMR:CDCl<sub>3</sub> <sup>1</sup>H δ (ppm) 3.10 (s,6H); 5.10 (s,2H); 5.55 (s,1H); 6.50 (s,1H); 7.2-7.30 (m,3H); 7.40-7.50 (m,2H); 8.50 (bs,1H)

**Step 3 : 1-Benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde dimethylhydrazone**

25

- To a stirred solution of 2.3 g (8.45 mmol) of the compound obtained in the preceding Step 2 in 58 ml of anhydrous DMF are added 2.3 ml (2.0 g, 1.69 mmol) of *N,N'*-dimethylformamide acetal. The reaction mixture is maintained at 100°C for 10 minutes and concentrated under vacuum. The residue is taken up in dichloromethane and the product is precipitated by addition of ether to provide 1.75 g (yield:72.3%) of the desired compound.
- 5 NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.20 (s,6H); 3.50 (s,3H); 5.15 (s,2H); 6.10 (s,1H); 6.60 (s,1H); 7.2-7.30 (m,3H); 7.40-7.50 (m,2H)

**Step 4: Methyl 1-benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-(carbaldehyde dimethylhydrazone)-5-carboxylate**

- 10 To a stirred solution of 1.7 g (5.94 mmol) of the compound obtained in the preceding Step 3 in 61 ml of anhydrous acetonitrile are added successively 1.68 g (7.1 mmol) of  $\text{Pd}(\text{OAc})_2$  and 0.613 g (7.1 mmol) of methyl acrylate. After 20 minutes of stirring under reflux the reaction mixture is filtered off and concentrated under vacuum. The residue is chromatographed over silica gel (dichloromethane/methanol : 97/3) to provide 1.40 g
- 15 (yield:63.6%) of the desired compound.
- NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.20 (s,6H); 3.55 (s,3H); 3.75 (s,3H); 5.20 (s,2H); 6.70 (s,1H); 7.1-7.70 (m,7H).

**Step 5: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid methyl ester**

- 20 A solution of 1.4 g (3.78 mmol) of the compound obtained in the preceding Step 4, 18 ml of chlorobenzene and 3.6 ml of acetic acid is stirred under reflux for 3 hours, and concentrated under vacuum to provide 1.4 g of a precipitate. The desired compound (0.76 g; yield:62%) is obtained by recrystallization of the crude product in 120 ml of ethyl acetate.
- 25 NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.70 (s,3H); 4.0 (s,3H); 5.30 (s,2H); 7.2-7.35 (m,3H); 7.45-7.55 (m,2H); 8.80 (s,1H); 8.85 (s,1H).

**Step 6: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid**

0.76 g (2.34 mmol) of the compound obtained in the preceding Step 5, 7.6 ml of methanol, 7.6 ml of water and 0.646 g (4.67 mmol) of  $K_2CO_3$  are stirred overnight at room temperature and then heated to reflux for 5 minutes. After cooling and addition of water the acidification to pH 1 of the mixture provides a precipitate which is dissolved in a mixture of methanol/dichloromethane. The organic layer is washed with water, dried and concentrated under vacuum. The residue obtained is concretized in a mixture of dichloromethane/ether to give 0.54 g (yield: 74%) of the desired compound.

NMR: DMSO  $^1H$   $\delta$  (ppm) 3.60 (s, 3H); 5.20 (s, 2H); 7.2-7.40 (m, 5H); 8.50 (s, 1H); 9.0 (s, 1H); 13.3 (bs, 1H)

M.P. = 240°C

HPLC = 100%

**Step 7: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 6 and piperonylamine.

TLC :  $CH_2Cl_2$  / MeOH 95/5  $R_f$  = 0.60

NMR: DMSO  $^1H$   $\delta$  (ppm): 3.65 (s, 3H); 4.40 (d, 2H); 5.15 (s, 2H); 5.95 (s, 2H); 6.75-6.85 (m, 2H); 6.90 (s, 1H); 7.2-7.40 (m, 5H); 8.45 (s, 1H); 8.90 (s, 1H); 9.25 (t, 1H).

IR : 3387, 1716, 1662, 14875, 1442, 1250, 1239, 1040, 789  $cm^{-1}$

M.P. = 197.5 °C

HPLC : 100 %

**Example 168 : Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate**

**Step 1 : 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid**

3.3 g (10.6 mmol) of the compound obtained in the Step 6 of Example 167 are treated according to the procedure described in the Step 1 of Example 164 to give 2.0 g (yield: 85.3%) of the desired compound.



NMR:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 8.40 (s,1H); 8.95 (s,1H); 12.0 (s,1H); 12.90 (bs,1H)

HPLC = 100%

5                    **Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained (yield: 78%) according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxybenzylamine.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.50

10                    NMR:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 6.85 (dd,2H); 7.25 (dd,2H); 8.40 (s,1H); 8.85 (s,1H); 9.20 (t,1H); 12.0 (s,1H)

HPLC = 99 %

**Step 3: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate**

15                    The compound is obtained (0.2 g; yield:77%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate.

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 95/5  $R_f$  = 0.80

20                    NMR:DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s,3H); 3.70 (s,3H); 3.85 (s,3H); 4.50 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.20 (d,2H); 7.50 (d,2H); 7.90 (d,2H); 8.5 (s,1H); 8.90 (s,1H); 9.20 (t,1H)

IR : 3396, 1719, 1661, 1439, 1279, 1250, 1110, 753  $\text{cm}^{-1}$

M.P. = 211.1  $^{\circ}\text{C}$

HPLC : 99.5 %

25                    **Example 169: tert-Butyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate**

The compound is obtained (yield: 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of example 168 and *tert*-butyl 4-bromomethyl-benzoate.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.80

- 5 NMR: DMSO <sup>1</sup>H δ (ppm): 1.50 (s, 9H); 3.65 (s, 3H); 3.75 (s, 3H); 4.40 (d, 2H); 5.20 (s, 2H); 6.85 (dd, 2H); 7.25 (dd, 2H); 7.45 (dd, 2H); 7.85 (dd, 2H); 8.50 (s, 1H); 8.90 (s, 1H); 9.2 (t, 1H);  
HPLC = 98 %

10 **Example 170: 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide**

The compound is obtained (yield: 62.4%) according to the procedure of the Example 1 using the compound obtained in the Step 1 of Example 168 and 3-methoxybenzylamine.

- 15 TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.50  
NMR: DMSO <sup>1</sup>H δ (ppm): 3.60 (s, 3H); 3.75 (s, 3H); 4.50 (d, 2H); 6.75-6.95 (m, 3H); 7.20-7.30 (m, 1H); 8.40 (s, 1H); 8.85 (s, 1H); 9.25 (t, 1H); 12.0 (s, 1H)  
HPLC = 98 %

20 **Step 2: *tert*-Butyl 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate**

The compound is obtained (yield: 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and *tert*-butyl 4-(bromomethyl)benzoate.

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.80

- 25 NMR: DMSO <sup>1</sup>H δ (ppm): 1.50 (s, 9H); 3.65 (s, 3H); 3.75 (s, 3H); 4.50 (d, 2H); 5.20 (s, 2H); 6.80-6.95 (m, 3H); 7.20-7.30 (m, 1H); 7.5 (dd, 2H); 7.85 (dd, 2H); 8.50 (s, 1H); 8.95 (s, 1H); 9.3 (t, 1H);  
HPLC = 93.6 %

**Step 3: 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid**

The compound is obtained according to the procedure of the Step 2 of Example 169 using the compound obtained in the preceding Step 2.

- 5     **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.60  
      **NMR**: DMSO <sup>1</sup>H δ (ppm): 3.65 (s,3H); 3.75 (s,3H); 4.50 (d,2H) ; 5.20 (s,2H) ; 6.75-6.80 (s,1H); 6.90 (s,2H); 7.20-7.25 (m,1H); 7.45 (d,2H); 7.85 (d,2H); 8.5 (s,1H); 8.90 (s,1H); 9.30 (t,1H); 12.95 (bs,1H)  
      **IR** : 3378, 1712, 1660, 1600, 1439, 1266, 1056, 790 cm<sup>-1</sup>  
10    **M.P.** = 208.1 °C  
      **HPLC** : 96.6 %

**Example 171: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

- 15    The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of Example 168 and (4-bromomethyl)-benzonitrile

**TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.80  
      **NMR**: DMSO <sup>1</sup>H δ (ppm): 3.65 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,2H); 7.80 (d,2H); 8.5 (s,1H); 8.95 (s,1H); 9.20 (t,1H).  
      **IR** : 3391, 2228, 1716, 1662, 1443, 1331, 1251, 789 cm<sup>-1</sup>  
20    **M.P.** = 230 °C  
      **HPLC** : 98.8 %

**Example 172: 3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1H-quinazoline-2,4-dione**

- 25    The compound of the preparation C is treated by SOCl<sub>2</sub> in THF to give its chloride derivate which is reacted with phenetyl magnesium bromide and CuI in presence of THF. After usual treatment the desired compound is obtained.

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.0 (m, 2H); 3.30 (m, 2H); 3.60 (s, 3H); 5.25 (s, 2H); 7.10-7.35 (m, 9H); 7.50 (m, 2H); 8.3 (m, 1H); 8.80 (s, 1H)

M.P. = 155 °C

HPLC : 98.0 %

5     **Example 173: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester**

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm) 3.60 (s, 3H); 5.0 (d, 2H); 5.30 (s, 2H); 6.5-6.7 (m, 2H); 7.15-7.35 (m, 6H); 7.55 (m, 2H); 8.40 (m, 1H); 8.60 (m, 2H); 9.0 (s, 1H)

M.P. = 147 °C

10     HPLC : 97.5 %

**Example 174: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester**

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.60 (s, 3H); 5.0 (d, 2H); 5.30 (s, 2H); 6.5 (m, 1H); 6.8 (d, 1H); 7.30 (m, 5H); 7.60 (m, 2H); 7.7 (d, 1H); 8.40 (d, 1H); 8.55 (m, 1H); 8.70 (s, 1H); 9.0 (s, 1H)

15     M.P. = 184 °C

HPLC : 99.6 %

**Example 175: 3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1*H*-quinazoline-2,4-dione**

TLC :  $\text{CH}_2\text{Cl}_2$  / MeOH 98/2  $R_f$  = 0.20

20     NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 3.65 (s, 3H); 4.45 (s, 2H); 5.25 (s, 2H); 7.18 (d, 2H); 7.20-7.35 (m, 4H); 7.50 (d, 2H); 8.3 (d, 1H); 8.40 (d, 2H); 8.80 (s, 1H).

IR : 1706, 1693, 1657, 1610, 1574, 1508, 1480, 1448, 1428, 1321, 1307, 1206, 1093, 831, 810, 782, 703  $\text{cm}^{-1}$

M.P. = 187 °C

25     HPLC : 98.0 %

**Example 176: 3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained by catalytic hydrogenation of the compound of Example 60 using Raney Ni and NH<sub>3</sub> in methanol.

5     **TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH / NH<sub>4</sub>OH 90/10 /1 R<sub>f</sub> = 0.25

**NMR**: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 1.45-1.70 (m, 2H) ; 3.6 (s, 3H) ; 3.8 (m, 5H) ; 4.55 (d, 2H) ; 5.22 (s, 2H) ; 6.74 (m, 1H) ; 6.86 (d, 2H) ; 7.2-7.30 (m, 5H) ; 7.44 (d, 2H) ; 8.28 (d, 1H) ; 8.48 (s, 1H)

10     **IR** : 3370, 1702, 1655, 1640, 1617, 1542, 1508, 1477, 1324, 1303 ; 1247, 1173, 1032, 829, 786, 756 cm<sup>-1</sup>

**M.P.** = 187 °C

**HPLC** : 98.4%

**Example 177: 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

15     The compound is obtained according to the procedure of the Step 2 of Example 34 using 2-(4-bromomethylphenyl)-benzonitrile.

**TLC** : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 98.5/1.5 R<sub>f</sub> = 0.20

20     **NMR**: CDCl<sub>3</sub> <sup>1</sup>H δ (ppm): 3.65 (s, 3H) ; 3.80 (s, 3H) ; 4.55 (d, 2H) ; 5.30 (s, 2H) ; 6.55-6.65 (m, 1H) ; 6.25 (d, 2H) ; 7.2-7.30 (m, 3H) ; 7.35-7.50 (m, 4H) ; 7.55-7.65 (m, 3H) ; 7.75 (d, 1H) ; 8.25-8.35 (m, 1H) ; 8.45 (s, 1H)

**IR** : 1702, 1661, 1629, 1508, 1478, 1332, 1242, 1036, 833, 766 cm<sup>-1</sup>

**M.P.** = 200 °C

**HPLC** : 99.8 %

25     **Example 178: 1-Methyl-2,4-dioxo-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using 5-[(4-bromomethyl)biphenyl]-tetrazole.

TLC: CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.50

5 NMR: DMSO <sup>1</sup>H δ (ppm): 3.55 (s, 3H); 3.75 (s, 3H); 4.40 (d, 2H); 5.15 (s, 2H); 6.90 (d, 2H); 7.05 (d, 2H); 7.25 (d, 4H); 7.45-7.70 (m, 6H); 8.30 (d, 1H); 8.6 (s, 1H); 9.25 (m, 1H)

IR: 2943, 1702, 1656, 1618, 1510, 1477, 1450, 1323, 1302, 1247, 1032, 829, 814, 782, 757 cm<sup>-1</sup>

HPLC: 99.6 %

10 **Example 179: Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethylphenyl)benzoate

TLC: CH<sub>2</sub>Cl<sub>2</sub> / MeOH 97/3 R<sub>f</sub> = 0.30

15 NMR: DMSO <sup>1</sup>H δ (ppm): 3.61 (s, 3H); 3.62 (s, 3H); 3.80 (s, 3H); 4.55 (d, 2H); 5.30 (s, 2H); 6.65 (t, 1H); 6.85 (d, 2H); 7.2-7.30 (m, 6H); 7.35-7.40 (m, 1 H); 7.45-7.55 (m, 3H); 7.80 (d, 1H); 8.27 (d, 1H); 8.47 (s, 1H)

IR: 1707, 1668, 1656, 1638, 1616, 1509, 1478, 1330, 1294, 1248, 1089, 765, 754 cm<sup>-1</sup>

M.P. = 172 °C

20 HPLC: 99.7 %

**Example 180: 4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid**

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 179.

25 TLC: CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.40

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.57 (s, 3H); 3.72 (s, 3H); 4.42 (d, 2H); 5.20 (s, 2H); 6.90 (d, 2H); 7.25-7.45 (m, 8H); 7.50-7.60 (m, 2H); 7.70 (d, 1H); 8.26 (d, 1H); 8.60 (s, 1H); 9.17-9.27 (m, 1H); 12.5-13.2 (m, 1H)

IR: 1698, 1668, 1655, 1639, 1612, 1508, 1479, 1330, 1304, 1248, 765, 754  $\text{cm}^{-1}$

5 M.P. = 175 °C

HPLC: 100 %

**Example 181: Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethyl)-2-fluoro-benzoate.

TLC:  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.60

NMR:  $\text{CDCl}_3$   $^1\text{H}$   $\delta$  (ppm): 1.30 (t, 3H); 3.60 (s, 3H); 3.80 (s, 3H); 4.35 (q, 2H); 4.60 (m, 2H); 5.30 (s, 2H); 6.55 (m, 1H); 6.90 (m, 2H); 7.30 (m, 5H); 7.90 (m, 1H); 8.30 (m, 1H); 8.50 (s, 1H);

15 M.P. = 156 °C

HPLC: 100 %

**Example 182: 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

20 The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 181.

TLC:  $\text{CH}_2\text{Cl}_2$  / MeOH 90/10  $R_f$  = 0.20

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.60 (s, 3H); 3.75 (s, 3H); 4.40 (m, 2H); 5.20 (s, 2H); 6.90 (m, 2H); 7.30 (m, 4H); 7.60 (d, 1H); 7.80 (m, 1H); 8.30 (m, 1H); 8.70 (s, 1H); 9.2 (s, 1H); 13.2 (s, 1H)

25 M.P. = 160 °C

HPLC: 100 %

**Example 183: 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester**

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.20

5 NMR: CDCl<sub>3</sub> <sup>1</sup>H δ ( ppm ) 2.3 (s, 6H) ; 2.60 (m, 2H) ; 3.60 (s, 3H) ; 3.75 (s, 3H) ; 3.85 (s, 3H) ; 4.35 (m, 2H) ; 4.55 (m, 2H) ; 5.25 (s, 2H) ; 6.50 (m, 1H) ; 6.80 (m, 2H) ; 7.10 (d, 1H) ; 7.25 (m, 4H) ; 7.70 (d, 1H) ; 8.25 (m, 1H) ; 8.5 (s, 1H)

M.P. = 130 °C

HPLC : 97.3 %

10 **Example 184: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylamino-ethyl ester**

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.60

15 NMR: CDCl<sub>3</sub> <sup>1</sup>H δ ( ppm ) 2.3 (s, 6H) ; 2.55 (s, 3H) ; 2.70 (m, 2H) ; 3.60 (s, 3H) ; 3.80 (s, 3H) ; 4.40 (m, 2H) ; 4.60 (m, 2H) ; 5.20 (s, 2H) ; 6.60 (s, 1H) ; 6.80 (m, 2H) ; 7.30 (m, 5H) ; 7.80 (m, 1H) ; 8.30 (m, 1H) ; 8.5 (s, 1H)

M.P. = 146 °C

HPLC : 99 %

20 **Example 185: 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

TLC : CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.30

25 NMR: DMSO <sup>1</sup>H δ ( ppm ) 3.2 (m, 1H) ; 3.55 (s, 3H) ; 3.70 (s, 3H) ; 4.40 (d, 2H) ; 5.20 (s, 2H) ; 6.90 (m, 2H) ; 7.25 (m, 2H) ; 7.40 (m, 2H) ; 7.55 (m, 1H) ; 7.70 (m, 2H) ; 8.30 (m, 1H) ; 8.60 (s, 1H) ; 9.2 (m, 1H)

M.P. = 305 °C



HPLC : 100 %

**Example 186: {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-phenyl}-acetic acid**

- 5     **TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 90/10 R<sub>f</sub> = 0.35  
NMR: DMSO <sup>1</sup>H δ ( ppm ) 3.50 (m, 5H) ; 3.70 (s, 3H) ; 4.40 (d, 2H) ; 6.80 (d, 2H) ; 7.20 (m, 4H) ; 7.40 (d, 2H) ; 7.60 (d, 1H) ; 8.30 (d, 1H) ; 8.60 (s, 1H) ; 9.2 (t, 1H)  
IR = 1717, 1645, 1619, 1501, 1298, 1240, 823, 750  
HPLC : 100 %

- 10     **Example 187: 1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

- TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.58  
NMR: DMSO <sup>1</sup>H δ ( ppm ) 2.0 (d, 3H) ; 3.45 (s, 3H) ; 4.40 (d, 2H) ; 6.00 (s, 2H) ; 6.80-6.95 (m, 4H) ; 7.4-7.50 (m, 3H) ; 7.55 (t, 1H) ; 7.85-8.0 (m, 4H) ; 8.20 (d, 1H) ; 8.6 (s, 1H) ; 9.15 (t, 1H)  
15     **IR :** 1656, 1618, 1503, 1440, 1254, 1040, 777, 754 cm<sup>-1</sup>  
         **M.P. =** 157 °C  
         **HPLC :** 96.2 %

- 20     **Example 188 :4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid**

- To a stirred solution of 0.5 g (0.9 mmol) of the compound obtained in the Example 169 in 50 ml of dichloromethane are added 5 ml of trifluoroacetic acid. The mixture is stirred overnight at room temperature and 60 ml of ether are added. The product crystallizes and after filtration 0.44 g (yield: 100%) of the desired compound is obtained.  
25     **TLC :** CH<sub>2</sub>Cl<sub>2</sub> / MeOH 95/5 R<sub>f</sub> = 0.60

NMR: DMSO  $^1\text{H}$   $\delta$  (ppm): 3.65 (s, 3H); 3.75 (s, 3H); 4.45 (d, 2H); 5.25 (s, 2H); 6.90 (d, 2H); 7.25 (d, 2H); 7.50 (d, 2H); 7.90 (d, 2H); 8.5 (s, 1H); 8.95 (s, 1H); 9.20 (t, 1H); 12.85 (bs, 1H)

IR : 3388, 1715, 1662, 1475, 1442, 1247, 791  $\text{cm}^{-1}$

M.P. = 264.4  $^{\circ}\text{C}$

5 HPLC : 98.9 %

**Example 189 : 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

10 To 0.5 g (1.5 mmol) of the compound of Preparation D in dimethylformamide (10 ml) are added EDAC.HCl 0.38g (1.9 mmol), HOBT 0.27 g (1.9 mmol), followed by 4-pyridyl-benzylamine 0.21 g (1.9 mmol). The mixture is stirred 48 hours at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried  $\text{MgSO}_4$ . recrystallized solid product in hot ethyl acetate to obtain 0.13 g (yield: 20%) of  
15 the desired compound.

MS:  $m/z$  (APCI, AP+) 419.2  $[\text{M}]^+$

CHN Analysis: Calcd (%) : C, 66.02; H, 4.58; N, 13.39.

Found (%) : C, 65.73; H, 4.47; N, 13.36.

20 **Example 190: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

0.10 g (yield: 17%) of the desired compound is obtained according to the procedure of Example 189, but using 2-methoxy-4-pyridyl-benzylamine.

MS:  $m/z$  (APCI, AP+) 449.2  $[\text{M}]^+$

25 CHN Analysis:  $\text{C}_{24}\text{H}_{21}\text{FN}_4\text{O}_4 \cdot 0.1 \text{H}_2\text{O}$

Calcd (%) : C, 64.02; H, 4.75; N, 12.44.

Found (%) : C, 63.66; H, 5.07; N, 12.16.

**Example 191: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

0.11 g (yield : 26%) of the desired compound is obtained according to the procedure of Example 189, but using 3-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 419.1 [M]<sup>+</sup>

CHN Analysis: C<sub>23</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>3</sub> 1.2 H<sub>2</sub>O

5 Calcd (%) : C, 62.78; H, 4.90; N, 12.73.

Found (%) : C, 62.75; H, 4.90; N, 12.73.

**Example 192: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

10 0.12 g (yield: 35%) of the desired compound is obtained according to the procedure of Example 189, but using 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 448.1 [M]<sup>+</sup>

CHN Analysis: C<sub>25</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> 0.1 H<sub>2</sub>O

Calcd (%) : C, 66.84; H, 4.98; N, 9.35.

Found (%) : C, 66.57; H, 4.83; N, 9.03.

15 **Example 193: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide**

0.20 g (yield : 59%) of the desired compound is obtained according to the procedure of Example 189, but using 3-methoxy-benzylamine.

MS: m/z (APCI, AP+) 448.1 [M]<sup>+</sup>

20 CHN Analysis: C<sub>25</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub>

Calcd (%) : C, 67.11; H, 4.96; N, 9.39.

Found (%) : C, 66.82; H, 4.87; N, 9.11.

**Example 194 : 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

0.13 g (yield : 20%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of the Preparation E and 4-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 433.2 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 66.66; H, 4.89; N, 12.96.

5 Found (%) : C, 66.26; H, 4.71; N, 12.78.

**Example 195: 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

0.18 g (yield : 51%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of Preparation E and 3-pyridyl-benzylamine.

10 MS: m/z (APCI, AP+) 433.1 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 66.66; H, 4.89; N, 12.96.

Found (%) : C, 66.43; H, 5.03; N, 12.84.

**Example 196: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

15 **Step 1: Methyl 3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

4.6 g (yield : 59%) of the desired compound is obtained according to the procedure of Step 1 of Preparation D, but using 4-bromobenzyl isocyanate.

MS: m/z (APCI, AP+) 388.9 [M]<sup>+</sup>

20 CHN Analysis: Calcd (%) : C, 52.46; H, 3.37; N, 7.20.

Found (%) : C, 52.16; H, 3.30; N, 7.30.

**Step 2: Methyl 1-methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

1.49 g (yield : 71%) of the desired compound is obtained according to the procedure of step 2 of Preparation D, but using the compound obtained in the Preceding Step 1.

25

MS: m/z (APCI, AP+) 404.9 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 53.62; H, 3.75; N, 6.95.

Found (%) : C, 53.24; H, 3.71; N, 6.84.

**Step 3: 1-Methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

1.3 g (yield : 87%) of the desired compound is obtained according to the procedure of Step 2-4 of Preparation B, but using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 388.9 [M]<sup>+</sup>

CHN Analysis: Calcd (%) : C, 52.46; H, 3.37; N, 7.20.

Found (%) : C, 52.12; H, 3.30; N, 7.11.

**Step 4: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

0.24 g (yield : 76%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 508 [M]<sup>+</sup>

CHN Analysis: C<sub>25</sub>H<sub>22</sub>BrN<sub>3</sub>O<sub>4</sub> 0.2 H<sub>2</sub>O

Calcd (%) : C, 58.65; H, 4.41; N, 8.21.

Found (%) : C, 58.32; H, 4.32; N, 8.12.

**Example 197: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

0.22 g (yield : 33%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 2-methoxy-4-pyridyl-benzylamine.

NMR: DMSO <sup>1</sup>H δ (ppm): 3.52 (3H,s); 3.79 (3H,s); 4.43 (2H,d); 5.09 (2H,s); 6.66 (1H,s); 6.89 (1H,d); 7.26-7.56 (5H,m); 8.06 (1H,d); 8.24-8.26 (1H,m); 8.61(1H,m); 9.31 (1H,t).

MS: m/z (APCI, AP+) 509 [M]<sup>+</sup>

**Example 198: 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

**Step 1: Methyl 3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

The compound is obtained with 51% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3,4-difluorobenzylamine.

NMR: DMSO  $^1\text{H}$  (ppm): 3.86 (3H,s); 5.05 (2H,s); 6.66 (1H,s); 7.18-7.43 (4H,m); 8.18 (1H,dd); 8.47 (1H,s).

MS: m/z (APCI, AP+) 347.1  $[\text{M}]^+$

**Step 2 : Methyl 1-methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

1.5 g (yield : 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1.

MS: m/z (APCI, AP+) 361.0  $[\text{M}]^+$

CHN Analysis: Calcd (%) : C, 60.00; H, 3.92; N, 7.77.

Found (%) : C, 60.05; H, 3.85; N, 7.72.

**Step 3: 1-Methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

1.1 g (yield : 82%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 437.0  $[\text{M}]^+$

CHN Analysis: Calcd (%) : C, 58.96; H, 3.49; N, 8.09.

Found (%) : C, 58.67; H, 3.99; N, 7.27.

**Step 4: 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

0.48 g (yield : 79%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 3-pyridylbenzylamine.

MS: m/z (APCI, AP+) 437.1  $[\text{M}]^+$

**CHN Analysis:** C<sub>23</sub>H<sub>18</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub> 0.2 H<sub>2</sub>O

Calcd (%) : C, 62.78; H, 4.21; N, 12.73.

Found (%) : C, 62.50; H, 4.13; N, 12.82.

5                   **Example 199 : 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

0.23 g (yield : 38%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-pyridyl-benzylamine.

**MS:** m/z (APCI, AP+) 437.1 [M]<sup>+</sup>

10                   **CHN Analysis:** C<sub>23</sub>H<sub>18</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub>

Calcd (%) : C, 63.30; H, 4.16; N, 12.84.

Found (%) : C, 63.19; H, 4.07; N, 12.81.

**Example 200 : 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

15                   0.11 g (yield : 39%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-methoxy-benzylamine.

**MS:** m/z (APCI, AP+) 466.2 [M]<sup>+</sup>

**CHN Analysis:** C<sub>25</sub>H<sub>21</sub>F<sub>2</sub>N<sub>3</sub>O<sub>4</sub>

20                   Calcd (%) : C, 64.51; H, 4.55; N, 9.03.

Found (%) : C, 64.41; H, 4.53; N, 8.87.

**Example 201: 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

25                   **Step 1: Methyl 3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

The compound is obtained with 18.1% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3-chloro-4-fluorobenzylamine.

MS: m/z (APCI, AP<sup>+</sup>) 361.0 [M]<sup>+</sup>

5           **Step 2 : Methyl 1-methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

0.5 g (yield : 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1.

MS: m/z (APCI, AP<sup>+</sup>) 377.0 [M]<sup>+</sup>

10    **CHN Analysis:**    Calcd (%) : C, 57.38; H, 3.75; N, 7.44.  
                          Found (%) : C, 57.34; H, 3.73; N, 7.27.

**Step 3: 1-Methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

0.45 g (yield : 92%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2.

15

MS: m/z (APCI, AP<sup>+</sup>) 363.0 [M]<sup>+</sup>

**CHN Analysis:**    Calcd (%) : C, 56.29; H, 3.33; N, 7.72.  
                          Found (%) : C, 56.24; H, 3.21; N, 7.64.

**Step 4:    3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

20

0.17 g (yield : 69%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-pyridyl-benzylamine.

MS: m/z (APCI, AP<sup>+</sup>) 453.1 [M]<sup>+</sup>

25    **CHN Analysis:** C<sub>23</sub>H<sub>18</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub> · 1.1 H<sub>2</sub>O

Calcd (%) : C, 58.44; H, 4.31; N, 11.85.

Found (%) : C, 58.23; H, 4.23; N, 11.75.



**Example 202 : 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

0.21 g (yield : 80%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 201 and 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 482.1 [M]<sup>+</sup>

CHN Analysis: C<sub>25</sub>H<sub>21</sub>ClFN<sub>3</sub>O<sub>4</sub>

Calcd (%) : C, 62.31; H, 4.39; N, 8.72.

Found (%) : C, 62.12; H, 4.37; N, 8.51.

**Example 203 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium**

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in hot methanol is added 0.22g (1.03 mmol) choline bicarbonate. The mixture is heated to reflux for 1 hour. Cool and concentrate. The resulting solid is recrystallized from ethanol to provide 0.41 g (yield: 68%) of the desired compound.

CHN Analysis: C<sub>31</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub> · 0.5 H<sub>2</sub>O

Calcd (%) : C, 63.58; H, 6.37; N, 9.57.

Found (%) : C, 63.32; H, 6.58; N, 9.57.

**Example 204: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt**

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and CaCl<sub>2</sub> 0.058 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 0.49 g (yield : 94%) of the desired compound.

CHN Analysis: C<sub>52</sub>H<sub>44</sub>CaN<sub>6</sub>O<sub>12</sub> · 1.0 H<sub>2</sub>O

Calcd (%) : C, 62.27; H, 4.62; N, 8.38.

Found (%) : C, 61.95; H, 4.70; N, 8.34.

5                   **Example 205 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-  
2H-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt**

10                   A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and MgCl<sub>2</sub> 0.052 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 0.49 g (yield : 96%) of the desired compound.

CHN Analysis: C<sub>32</sub>H<sub>44</sub>MgN<sub>6</sub>O<sub>12</sub> · 1.0 H<sub>2</sub>O

Calcd (%) : C, 63.26; H, 4.70; N, 8.51.

Found (%) : C, 63.07; H, 4.89; N, 8.50.

15                   **Example 206: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-  
6-carboxylic acid (pyridin-4-ylmethyl)-amide**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid  
(pyridazin-4-ylmethyl)-amide**

20                   To a suspension of compound of the Step 1 of the Example 33 (1.00 g, 4.54 mmol), EDAC (1.13 g, 5.90 mmol), HOBt (0.675 g, 5.00 mmol) in 20 ml of DMF is added a solution of 4-aminomethyl-pyridine (0.507 ml, 5.00 mmol). The light orange suspension is stirred at room temperature overnight. After 24 h, the reaction mixture is concentrated affording a offwhite solid. The solids are subsequently washed with 10 ml of ethyl acetate, saturated Na<sub>2</sub>CO<sub>3</sub>, and 10 ml of H<sub>2</sub>O to give 1.20 g (yield: 85.7%) of product.

MP: 141-145 °C

25                   MS(APCI+): m/z 309.1 (MH<sup>+</sup>).

**Step 2: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-  
quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

To a suspension of compound obtained in the preceding Step 1 (0.200 g, 0.645 mmol) in 6 ml of DMF is added  $\text{Cs}_2\text{CO}_3$  (0.630 g, 1.93 mmol). After stirring at room temperature for 30 min, a solution of 4-chlorobenzyl-bromide (0.132 g, 0.645 mmol) in 2 ml of DMF is added dropwise to the reaction mixture and stirred overnight. White solids (cesium salt) are filtered and the solution was concentrated. The resulting suspension is diluted with 10 ml of ethyl acetate and filtered again. The filtrate is concentrated and trituration with 10 ml of ethyl acetate gave 0.26 g (yield: 92.9%) of a white solid corresponding to the desired compound.

MP: 228-230 °C

10 **CHN Analysis:**  $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_3\text{Cl}_1$

Calcd (%) : C, 63.52; H, 4.40; N, 12.88.

Found (%) : C, 63.40; H, 4.41; N, 12.84.

**Example 207: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

15 0.2 g of the desired compound (yield: 74.1%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 2 4-fluorobenzyl bromide.

mp 210-212 °C;

**CHN Analysis:**  $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_3\text{F}_1$

Calcd (%) : C, 66.02; H, 4.58; N, 13.39

20 Found (%) : C, 65.74; H, 4.60; N, 13.03.

**Example 208: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

25 1.18 g of the desired compound (yield: 83.7%) is obtained according to the procedure of Step 1 of the Example 206, but using 3-aminomethyl pyridine.

MS(APCI+): m/z 309.1 (MH);

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 3.43 (s, 3H, NCH<sub>3</sub>), 4.47 (d, J=5.86 Hz, 2H, NCH<sub>2</sub>Ar), 7.31-7.34 (m, 1H, ArH), 7.48 (d, J=8.79 Hz, 1H, ArH), 7.70 (d, J=7.82 Hz, 1H, ArH), 8.20 (dd, J=8.79, 1.95 Hz, 1H, ArH), 8.42-8.43 (m, 1H, ArH), 8.53 (d, J=2.20 Hz, 2H, ArH), 9.30 (t, J=5.62, 1H, ArH), 11.65 (s, 1H, NH);

5

**Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

0.25 g of the desired compound (yield: 82.6%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

10

MP : 166-168 °C

Anal. Calcd for C<sub>23</sub>H<sub>19</sub>N<sub>4</sub>O<sub>3</sub>F<sub>1</sub>: C, 65.79; H, 4.60; N, 13.34. Found: C, 65.40; H, 4.40; N, 13.18.

15

**Example 209: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide**

0.25 g of the desired compound (yield: 89.3%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 208 and 4-chlorobenzyl bromide.

MP : 173-175 °C

20

Anal. (%) Calcd for C<sub>23</sub>H<sub>19</sub>N<sub>4</sub>O<sub>3</sub>Cl<sub>1</sub>: C, 62.77; H, 4.48; N, 12.73. Found: C, 62.39; H, 4.46; N, 12.71.

**Example 210: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide**

25

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide**

1.29 g of the desired compound (yield: 83.8%) is obtained according to the procedure of Example 206, Step 1, but using 3-methoxybenzyl amine.

MP: 235-238°C.

**Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide**

0.25 g of the desired compound (yield: 95%) is obtained according to the procedure of Example 206, Steps 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

**MP:** 176-178°C

**Anal. (%)** Calcd for  $C_{25}H_{22}N_3O_4F$ : C, 67.11; H, 4.96; N, 9.39. Found: C, 66.99; H, 4.99; N, 9.18.

**Example 211: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide**

0.25 g of the desired compound (yield: 92%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 210 and 4-chlorobenzyl bromide.

**MP:** 178-180 °C

**Anal. (%)** Calcd for  $C_{25}H_{22}N_3O_4Cl$ : C, 64.60; H, 4.79; N, 9.04. Found: C, 64.22; H, 4.72; N, 8.84.

**Example 212: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

**Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

1.00 g of the desired compound (yield: 76.9%) is obtained according to the procedure of Example 206, Step 1, but using (2-methoxy-pyridin-4-yl)-methylamine.

**MP:** 215-218 °C

**MS(APCI+):** m/z 339.1 (MH).

**Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

0.07 g of the desired compound (yield: 26.5%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

MP : 174-175 °C

- 5     Anal. (%) Calcd for  $C_{24}H_{21}N_4O_4F$ : C, 64.20; H, 4.73; N, 12.48. Found: C, 63.88; H, 4.73; N, 12.08.

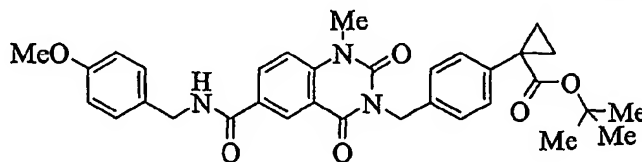
**Example 213: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

- 10     0.09 g of the desired compound (yield: 33%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in Step 1 of Example 212 and 4-chlorobenzyl bromide.

MP : 169-170 °C

- 15     Anal. (%) Calcd for  $C_{24}H_{21}N_4O_4Cl$ : C, 62.02; H, 4.61; N, 11.98. Found: C, 62.01; H, 5.01; N, 11.70.

**Example 214: tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate**



- 20     0.35 g of the desired compound (yield: 67%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 1 4-methoxy-benzylamine and in Step 2 tert-butyl 1-(4-bromomethyl-phenyl)-cyclopropanecarboxylate.

MP: 148-149 °C

Anal. (%) Calcd for  $C_{33}H_{35}N_3O_6$ : C, 68.88; H, 6.24; N, 7.30. Found: C, 68.49; H, 6.29; N, 7.21.

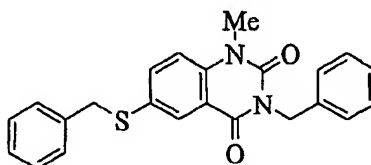
- 25     **Example 215: 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid**

To a solution of the compound of Example 214 (0.35 g, 0.61 mmol) in 2 ml of  $\text{CH}_2\text{Cl}_2$  are added 2 ml of TFA. The yellow solution is stirred at room temperature for 4 hours. The reaction mixture is concentrated and trituration with diethyl ether gives 0.25 g (yield: 79%) of a white solid corresponding to the desired compound.

5 **MP** : 179-181°C

**Anal.** (%) Calcd for  $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_6$ : C, 66.22; H, 5.35; N, 7.77. Found: C, 66.61; H, 5.40; N, 8.04.

**Example 216: 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione**



10 **Step 1: 5-Iodo-2-methylamino-benzoic acid**

To a solution of N-methylantranilic acid (5.00 g, 3.31 mmol) in 30 ml of acetic acid are added 60 ml of  $\text{H}_2\text{O}$  and  $\text{I}_2$  (8.39 g, 3.31 mmol) is added portionwise over a period of 5 minutes. The reaction mixture is stirred at room temperature for 2 days. After 48 hours, the product is filtered and washed with 30 ml of  $\text{H}_2\text{O}$ . The mother liquor is concentrated  
15 affording more product

**Weight**: 7.3 g; **Yield** = 80%

**MP**: 170-172 °C

**MS**(APCI+):  $m/z$  276.0 (MH).

**Step 2: 3-Benzyl-6-iodo-1-methyl-1H-quinazoline-2,4-dione**

20 To a mixture of the compound obtained in the preceding Step 1 (0.50 g, 1.9 mmol), isothiocyanate (0.236 g, 1.58 mmol), and  $\text{CF}_3\text{CO}_2\text{Ag}$  (0.838 g, 3.80 mmol) is added slowly  $\text{Et}_3\text{N}$ . The reaction mixture is heated at reflux for 1.5 hours. After cooled to room temperature, silver sulfide is filtered and the filtrate is concentrated affording a brown oil. The product is purified by chromatography on silica gel (ethyl acetate/hexane: 20/80) to  
25 give 0.300 g (48.0%) of a white solid

MP: 149-150°C

MS(APCI+): m/z 391.0 (MH<sup>+</sup>).

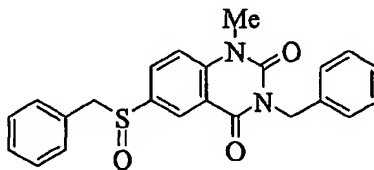
**Step 3: 3-Benzyl-6-benzylsulfonyl-1-methyl-1H-quinazoline-2,4-dione**

To a mixture of KHCO<sub>3</sub> (0.009 g, 0.089 mmol), PPh<sub>3</sub> (0.007 g, 0.027 mmol), n-Bu<sub>4</sub>NI  
5 (0.033 g, 0.089 mmol), Pd(OAc)<sub>2</sub> (0.002 g, 0.009 mmol), after purging with N<sub>2</sub> for 5 min,  
are added a solution of the compound of the preceding Step 2 (0.035 g, 0.089 mmol) and  
butyl-thiocarbamic acid S-benzyl ester (0.020 g, 0.089 mmol) in 5 ml of dioxane at room  
temperature. The brown solution is heated at 100°C for overnight. After 24 hours, the  
10 reaction mixture is cooled to room temperature and diluted with 20 ml of ethyl acetate,  
filtered through a sheet of celite, washed with H<sub>2</sub>O (2x5 ml), concentrated affording a  
yellow oil. Trituration with diethyl gives 0.025 g (yield: 72%) of a yellow solid  
corresponding to the desired compound.

MP: 117-118°C

Anal. (%) Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>: C, 69.66; H, 5.31; N, 7.06. Found: C, 69.26; H, 5.04;  
15 N, 6.93.

**Example 217: 3-Benzyl-1-methyl-6-phenylmethanesulfinyl-1H-quinazoline-2,4-dione**



To a solution of the compound of Example 216 (0.050 g, 0.129 mmol) in 9 ml of  
anhydrous CH<sub>2</sub>Cl<sub>2</sub> is added *m*-chloro-perbenzoic acid (0.029 g, 0.127 mmol) at -5°C. After  
20 stirring at -5°C for 3 hours, the reaction mixture is quenched with 20 ml of NaHCO<sub>3</sub> while  
in the ice-bath. The organic layer is separated and the aqueous is extracted with CH<sub>2</sub>Cl<sub>2</sub>  
(2x20 ml). The combined organic layers concentrated affording a yellow oil. The product  
is purified by chromatography on silica gel (ethyl acetate/hexane: 30/70) to give 0.070 g  
(yield: 33.7%) of a white solid corresponding to the desired compound.

25 MP: 182-183°C



Anal. (%) Calcd for  $C_{23}H_{20}N_2O_3S_1$ : C, 67.84; H, 5.03; N, 6.88. Found: C, 68.13; H, 4.86; N, 6.48.

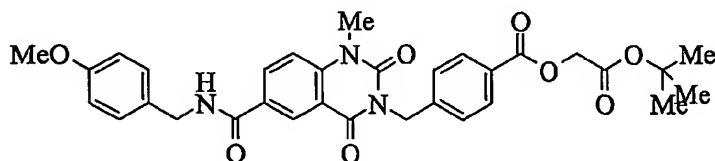
**Example 218 : 3-Benzyl-1-methyl-6-phenylmethanesulfonyl-1H-quinazoline-2,4-dione**

To a solution of the compound of Example 216 (0.133 g, 0.342 mmol) in 25 ml of anhydrous  $CH_2Cl_2$  is added *m*-chloro-perbenzoic acid (0.153 g, 0.685 mmol) at  $-5^\circ C$ . After stirring at  $-5^\circ C$  for 5 min, the ice-bath is removed and the reaction mixture is stirred at room temperature for 3 hours. The reaction is completed and quenched with 5 ml of saturated  $NaHCO_3$ . The organic layer is separated and the aqueous is extracted with  $CH_2Cl_2$  (2x20 ml). The combined organic layers concentrated affording a yellow oil. Trituration with ethyl acetate gives 0.80 g (yield: 56%) of a light yellow solid corresponding to the desired compound.

MP :  $173-175^\circ C$

Anal. (%) Calcd for  $C_{23}H_{20}N_2O_4S_1$ : C, 64.73; H, 4.89; N, 6.56. Found: C, 64.34; H, 4.72; N, 6.18.

**Example 219: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid tert-butoxycarbonylmethyl ester**

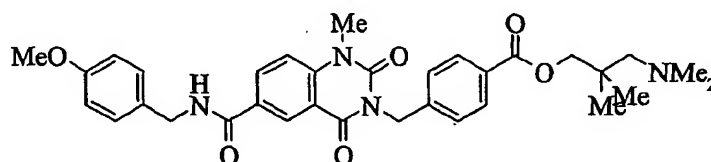


To 0.40 g (0.84 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.13g (1.0mmol) followed by tert-butylacetyl chloride 0.18 g (1.18 mmol). The mixture is stirred overnight at room temperature before concentrating in-vacuo, then diluted with ethyl acetate (20 ml). The organic layer is washed with saturated aqueous  $NaCl$  solution (2x20 ml), dried  $MgSO_4$ ; and purified by flash chromatography (EtOAc/ hexane eluent) to give 0.11 g (yield: 23%) of the desired compound.

MS:  $m/z$  (APCI, AP+) 588.4  $[M]^+$

CHN Analysis (%) :  $C_{32}H_{33}N_3O_8 \cdot 1.8 H_2O$  Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

**Example 220:** 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-dimethyl-propyl ester

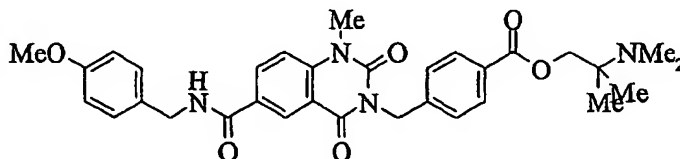


To 0.50 g (1.6 mmol) of compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by dimethylamino-dimethyl-propan-1-ol 0.27 g (2.1 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO<sub>4</sub>. The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl is added. After concentration and solidification in EtOAc, 0.49 g (yield: 43%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 587.0 [M]<sup>+</sup>

CHN Analysis (%):  $C_{33}H_{38}N_4O_6 \cdot 1.0 HCl \cdot 1.2 H_2O$  Calcd: C, 61.40; H, 6.48; N, 8.68. Found: C, 61.01; H, 6.31; N, 8.99.

**Example 221:** 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-methyl-propyl ester



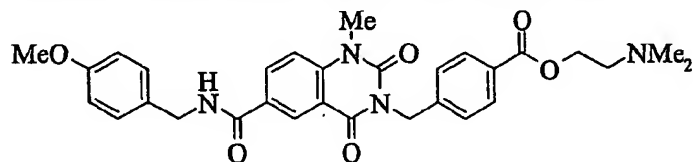
To 0.50 g (1.6 mmol) of the compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by

dimethylamino-methyl-propan-1-ol 0.24 g (2.1 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2x20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO<sub>4</sub>. The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl is added. After concentration and solidification in EtOAc, 0.21 g (yield: 21%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 573.2 [M]<sup>+</sup>

CHN Analysis (%): C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub> 1.0 HCl · 0.48 H<sub>2</sub>O Calcd: C, 62.22; H, 6.19; N, 9.07. Found: C, 61.82; H, 6.00; N, 9.16.

10 **Example 222: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-dimethylamino-ethyl ester**



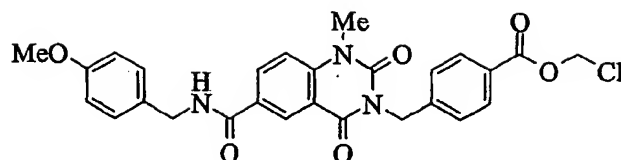
To 0.73 g (1.5 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added EDAC HCl 0.38g (2.0 mmol), HOBT 0.27 g (2.0 mmol), followed by dimethylamino-propan-1-ol 0.18 g (2.0 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (2 x 20 ml), and dried MgSO<sub>4</sub>. the crude product is solidified in EtOAc to give 0.49 g (yield: 60%) of the desired compound.

20 MS: m/z (APCI, AP+) 545.3 [M]<sup>+</sup>

CHN Analysis (%): C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub> 0.25 H<sub>2</sub>O Calcd: C, 65.62; H, 5.97; N, 10.20. Found: C, 65.62; H, 5.92; N, 10.23.

**Example 223: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid chloromethyl ester**

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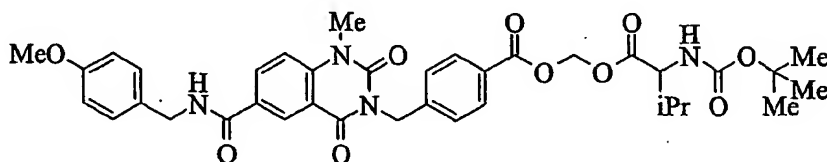


To 1.0 g (2.1 mmol) of the compound of Example 35 in dimethylformamide (15 ml) is di-isopropylethylamine 0.47g (3.6 mmol) followed by chloro-iodomethane 1.86 g (10.5 mmol). The mixture is stirred overnight at room temperature before diluting with ethyl acetate (20 ml). The organic layer is washed with water (1x10 ml) saturated aqueous NaCl solution (2x10 ml), and dried MgSO<sub>4</sub>. After solidification in ether 0.29 g (yield: 26%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 522.2 [M]<sup>+</sup>

CHN Analysis (%): C<sub>27</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>6</sub> Calcd: C, 62.13; H, 4.63; N, 8.05. Found: C, 62.08; H, 4.61; N, 7.95.

**Example 224: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-tert-butoxycarbonylamino-3-methyl-1-butanoyloxymethyl ester ester**

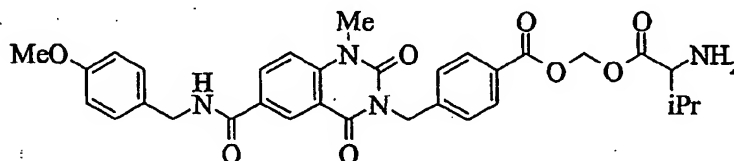


To 0.39 g (0.75 mmol) of the compound of Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.12g (0.96 mmol) followed by t-butoxycarbonyl-leucine 0.21 g (0.96 mmol). The mixture is stirred overnight at 60-70C for 12 hours, cooled and diluted with ethyl acetate (20 ml). The organic layer is washed with water (1 x 10 ml), 5% aqueous NaHCO<sub>3</sub> solution (1x10 ml), saturated aqueous NaCl (1x10 ml), dried MgSO<sub>4</sub>, and purified by flash chromatography (EtOAc/ hexane eluent) to give 0.14 g (yield: 25%) of the desired compound.

MS: m/z (APCI, AP+) 701.3 [M - Boc]<sup>+</sup>

CHN Analysis (%): C<sub>37</sub>H<sub>42</sub>N<sub>4</sub>O<sub>10</sub> Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

**Example 225: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-amino-3-methyl-butanoyloxymethyl ester hydrochloride**

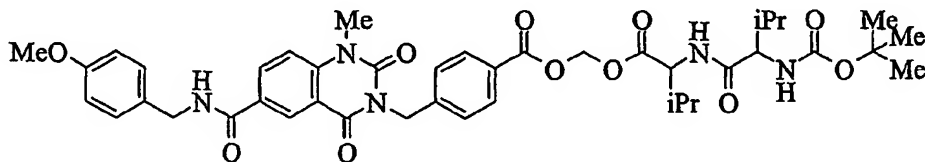


To 0.14 g (0.19 mmol) of the compound of Example 224 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.039 g (yield: 30%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 603.2 [M]<sup>+</sup>

CHN Analysis (%): C<sub>37</sub>H<sub>42</sub>N<sub>4</sub>O<sub>10</sub> Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

**Example 226: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester**



**Step 1: 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid methyl ester**

To 1.3 g (5.9 mmol) of t-butoxycarbonyl-leucine in dimethylformamide (15 ml) is added EDAC HCl 1.4g (7.1 mmol), HOBT 0.95 g (7.1 mmol), followed by NH<sub>2</sub>-Leu-OMe 1.0 g (5.9 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed

with 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (1 x 10 ml), saturated aqueous NaCl solution (2 x 20 ml), and dried MgSO<sub>4</sub>. A solidification in ether gives 1.05 g (yield: 53%) of the desired compound.

MS: m/z (APCI, AP+) 331.2 [M]<sup>+</sup>

CHN Analysis (%): C<sub>16</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> Calcd: C, 58.16; H, 9.15; N, 8.48. Found: C, 58.32; H, 9.24; N, 8.51.

**Step 2: 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid**

To 0.4 g (1.2 mmol) of the compound obtained in the preceding step 1, in 3:1:1 methanol/water/THF (10 ml) is added LiOH H<sub>2</sub>O, 0.06 g (1.44 mmol). The mixture is stirred overnight at room temperature. Partitioned between water (20 ml) and ethyl acetate (30 ml). The layers are separated and the aqueous layer made acidic with 2 M HCl. The product is extracted with EtOAc (2 x 20 ml) washed with saturated aqueous NaCl solution (1 x 20 ml), and dried MgSO<sub>4</sub>. A solidification in ether gives 0.22 g (yield: 58%) of the desired compound.

MS: m/z (APCI, AP+) 317.2 [M]<sup>+</sup>

CHN Analysis (%): C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> Calcd: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.72; H, 8.89; N, 8.64

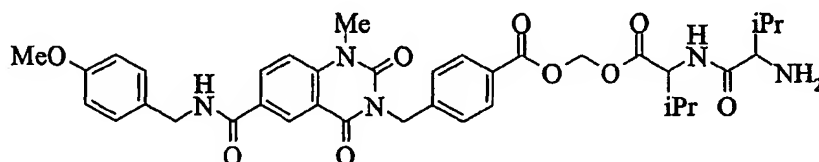
**Step 3: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester**

To 0.29 g (0.56 mmol) of the compound obtained in Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.092g (0.72 mmol) followed by compound obtained in the preceding Step 2, 0.23 g (0.72 mmol) then NaI (cat.). The mixture is stirred overnight at 50°C for 18 hours. Cool and dilute with water and extract with ethyl acetate (2 x 20 ml). The combined organic layer are washed with saturated aqueous NaHCO<sub>3</sub> solution (1 x 10 ml), saturated aqueous NaCl (3 x 10 ml) and dried MgSO<sub>4</sub>. a solidification in a mixture of EtOAc/hexane gives 0.27 g (yield: 63%) of the desired compound.

MS: m/z (APCI, AP+) 800.4 [M - Boc]<sup>+</sup>

CHN Analysis (%): C<sub>37</sub>H<sub>42</sub>N<sub>4</sub>O<sub>10</sub> Calcd: C, 62.91; H, 6.41; N, 8.73. Found: C, 62.59; H, 6.44; N, 8.39.

**Example 227: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester**



5 To 0.25 g (0.31 mmol) of compound of the Example 226 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.12 g (yield: 55%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 702.0 [M]<sup>+</sup>

10 **CHN Analysis (%)**: C<sub>37</sub>H<sub>43</sub>N<sub>5</sub>O<sub>9</sub> Calcd: C, 63.33; H, 6.18; N, 9.98. Found: C, 62.99; H, 6.06; N, 9.72.

**Examples 228 to 345:**

These compounds were obtained according to the procedure described in the Example 168 followed by the procedure of the Example 169.

15 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,  
 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,  
 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,  
 20 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,  
 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 5 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 15 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 ]pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 25 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,



- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 5 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 15 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 25 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 5 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 15 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 25 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 5 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 15 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 25 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 5 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 15 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 25 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 5 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
10 pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 15 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
20 pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 25 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 5 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 10 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 15 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 20 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 25 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,
- and 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]  
30 pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide.

**Examples 345 to 461:**

These compounds were obtained according to the procedure described for Example 131:

- 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 10 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 15 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 20 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 25 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 30 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 5 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,
- 10 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 15 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 20 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 25 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 30 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,



- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 10 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 15 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 20 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 25 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 30 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

5 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

10 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

15 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

20 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

25 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

30 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 5 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 10 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 15 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 20 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 25 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,
- 30 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

10 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

15 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

20 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

25 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

30 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

- 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 5 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 10 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 15 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,
- 20 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,
- 25 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,
- 30 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

5 and 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide.

#### **EXAMPLE 462**

##### **Evaluation of the *in vitro* activity of the compounds of formula (I) according to the invention.**

10 The ability of the compounds of formula (I) of the invention to inhibit matrix metalloprotease 13 was evaluated by measuring their IC<sub>50</sub> value (concentration required to inhibit 50% of the enzymatic activity) according to the protocol described below.

**MMP13CD Thiopeptolide Assay:** Proteolysis of the thiopeptolide substrate Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt is used as the primary screen to determine IC<sub>50</sub> values for  
15 MMP13 inhibitors. A 100 µl reaction contains 50 mM HEPES, 10 mM CaCl<sub>2</sub>, pH 7.0 (RT), 1 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 100 µM substrate, inhibitor in 2.0% DMSO and 2.5 nM human collagenase-3 catalytic domain enzyme. Inhibitors are screened from 100 µM to 0.5 nM. The change in absorbance at 405 nm is monitored on a microplate reader at room temperature continuously for 10-15 minutes. Percentage of  
20 control velocity in inhibited treatments is plotted against inhibitor concentration to calculate IC<sub>50</sub> values.

**Table 1**

Example	IC <sub>50</sub> (µM)	Example	IC <sub>50</sub> (µM)
1	0.193	26	0.009

2	0.183	27	1.7
3	0.021	28	0.017
4	1.87	29	0.003
5	0.366	30	0.026
6	0.049	31	0.157
7	0.167	32	0.6
8	1.32	33	0.75
9	0.005	34	0.004
10	0.057	35	0.001
11	2.25	36	0.028
12	0.042	37	0.029
13	0.012	38	0.031
14	0.051	39	0.011
15	0.7	40	0.004
16	0.015	41	0.007
17	0.009	42	0.0025
18	0.01	43	1.21
20	0.051	44	0.016
21	0.3	45	0.007
22	0.096	46	0.096
23	0.029	47	0.062
24	0.009	48	0.014
25	0.028		

Examination of the results of Table 1 shows that the products of the invention tested in the assay effectively inhibit matrix metalloprotease 13.

The protocol described above was also used to measure the activity of the compounds of the invention against MMP1, MMP2, MMP3, MMP7, MMP9, MMP12 and MMP14. The  
5 IC<sub>50</sub> values obtained on these MMPs were often greater than 100  $\mu$ M. These results indicate that the compounds of the invention are selective MMP13 inhibitors.

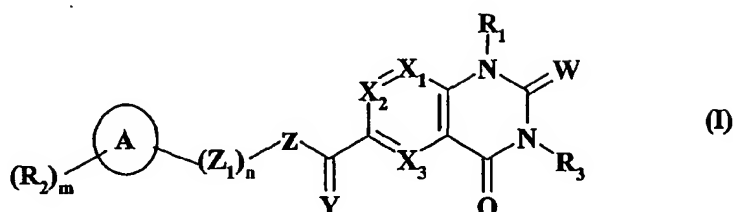
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5       investigational drugs, 2000, 2 (1), 16-25.



Claims

*I*-A compound selected from those of formula (I):



in which:

5  $R_1$  represents a group selected from :

- hydrogen, amino,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, mono $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, di $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, aryl, aryl $(C_1-C_6)$ alkyl, heterocycle, and 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino,  $(C_1-C_6)$ alkyl, cyano, halo $(C_1-C_6)$ alkyl,  $C(=O)OR_4$ ,  $OR_4$  and  $SR_4$ , in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl,

$W$  represents an oxygen atom, a sulphur atom, or a group  $=N-R'$ , in which  $R'$  represents  $(C_1-C_6)$ alkyl, hydroxyl, or cyano,

15  $X_1$ ,  $X_2$  and  $X_3$  represent, independently of each other, a nitrogen atom or a group  $-C-R_6$  in which  $R_6$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, amino, mono $(C_1-C_6)$ alkylamino, di $(C_1-C_6)$ alkylamino, hydroxyl,  $(C_1-C_6)$ alkoxy, and halogen, with the proviso that not more than two of the groups  $X_1$ ,  $X_2$  and  $X_3$  simultaneously represent a nitrogen atom,

20  $Y$  represents a group selected from oxygen atom, sulphur atom,  $-NH$ , and  $-N(C_1-C_6)$ alkyl,

$Z$  represents:

- an oxygen atom, a sulphur atom,

- or a group  $-NR_7$  in which  $R_7$  represents a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl, and heteroaryl, and
- when Y is an oxygen atom, a sulphur atom, or a group  $-N(C_1-C_6)alkyl$ , Z optionally represents a carbon atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl, an aryl, an aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

$Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  and  $R_9$ , independently of each other, represent a group selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, amino, OR<sub>4</sub>, SR<sub>4</sub> or C(=O)OR<sub>4</sub> in which  $R_4$  represents a hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and

- when n is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- and when one of the carbon atoms in the hydrocarbon chain  $Z_1$  is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group  $-C(=Y)-Z-$  optionally may be absent in the general formula (I),

A represents a group selected from :

- aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

m is an integer from 0 to 7 inclusive,

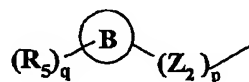
- the group(s)  $R_2$ , which may be identical or different, is (are) selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN, NO<sub>2</sub>, SCF<sub>3</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, SOR<sub>10</sub>, -SO<sub>2</sub>R<sub>10</sub>,

$-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  
 $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- $X_5$  represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or  $(C_1-C_6)$ alkyl,
- 5      •  $k$  is an integer from 0 to 3 inclusive,
- $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
- $X_4$  represents a group selected from single bond,  $-CH_2-$ , oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by  
 10      hydrogen atom or  $(C_1-C_6)$ alkyl group,
- $R_{12}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from  
 15      nitrogen, oxygen and sulphur;

$R_3$  represents a group selected from:

- hydrogen,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from  
 20      amino, cyano, halo $(C_1-C_6)$ alkyl, cycloalkyl,  $-C(=O)NR_{10}R_{11}$ ,  $-C(=O)OR_{10}$ ,  $OR_{10}$ , and  $SR_{10}$ , in which  $R_{10}$  and  $R_{11}$ , which may be identical or different, represent hydrogen or  $(C_1-C_6)$ alkyl,
- and the group of formula :



- 25      ✓ in which  $p$  is an integer from 0 to 8 inclusive,

- ✓  $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, phenyl, halo $(C_1-C_6)$ alkyl, halogen, amino,  $OR_4$ ,  $SR_4$  and  $-C(=O)OR_4$  in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl, and
- when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl, or a carbonyl group,
- ✓  $B$  represents a group selected from:
- an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
  - a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- ✓  $q$  is an integer from 0 to 7 inclusive,
- ✓ the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{18}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-R_{19}-C(=O)OR_{15}$ ,  $-X_6-R_{20}$ , and  $-C(=O)-R_{21}-NR_{15}R_{16}$  in which :
- $X_7$  represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a  $(C_1-C_6)$ alkyl group,
  - $k$  is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,
  - k2 is an integer from 1 to 4 inclusive,
  - R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 5       - R<sub>18</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, -R<sub>21</sub>-NR<sub>15</sub>R<sub>16</sub>, -R<sub>21</sub>-NR<sub>15</sub>-C(=O)-R<sub>21</sub>-NR<sub>16</sub>R<sub>17</sub>, and -C(=O)O-R<sub>21</sub>-NR<sub>15</sub>R<sub>16</sub> in which R<sub>21</sub> represents a linear or branched (C<sub>1</sub>-C<sub>6</sub>)alkylene group, and R<sub>15</sub>, R<sub>16</sub> and R<sub>17</sub> are as defined hereinbefore,
- R<sub>19</sub> represents a (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl group,
- 10       - X<sub>6</sub> represents a group selected from single bond, -CH<sub>2</sub>-, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C<sub>1</sub>-C<sub>6</sub>)alkyl group,
- R<sub>20</sub> represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups,
- 15       which may be identical or different, selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and -C(=O)OR<sub>4</sub> wherein R<sub>4</sub> represents hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- with the proviso that when X<sub>1</sub> represents a nitrogen atom, X<sub>2</sub> cannot represent a carbon atom substituted with a methyl group or with NH-CH<sub>3</sub>,
- 20       optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

2- A compound of formula (I) according to Claim 1 characterized in that:

- $R_1$  represents hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl or 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl,
  - W represents an oxygen atom or a sulphur atom,
  - $X_1$  represents a nitrogen atom or  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,
  - 5 •  $X_2$  and  $X_3$  represent each  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,
  - Y represents an oxygen atom,
  - Z represents an oxygen atom or  $-NR_7$  in which  $R_7$  represents a hydrogen atom,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 10 **3-** A compound of formula (I) according to Claim 1 characterized in that:  
n is an integer from 1 to 6 inclusive,

$Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  represents a hydrogen atom and  $R_9$  represents a hydrogen atom or a methyl group, and

- when n is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains a
- 15 double bond,
- or, one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, or a sulphur atom which is unsubstituted or substituted with one or two oxygens,

- A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, piperidyl,
- 20 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

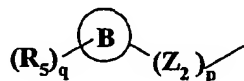
m is an integer from 0 to 7 inclusive,

- the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,
- 25  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- ✓  $X_5$  represents O, S or NH,
  - ✓  $k$  is an integer from 0 to 3 inclusive,
  - ✓  $R_{10}$  and  $R_{11}$ , identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
  - ✓  $X_4$  represents  $-CH_2-$ , or an oxygen atom,
  - 5 ✓  $R_{12}$  represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl and amino,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

10 4- A compound of formula (I) according to Claim 1 characterized in that:

$R_3$  represents hydrogen,  $(C_1-C_6)$ alkyl or the group of formula:



- in which  $p$  is an integer from 0 to 3 inclusive,
- $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen, methyl, or phenyl, and
- 15 • when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two
- 20 oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl, or a carbonyl group,
- $B$  represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl, and indolyl,
- 25 -  $q$  is an integer from 0 to 3 inclusive,

- the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-(CH_2)_kC(=O)NR_{15}R_{16}$  in which :
- $X_7$  is S, O or  $NH$ ,
  - $k$  is an integer from 0 to 3 inclusive,
  - $k_1$  is an integer from 0 to 2 inclusive,
  - $k_2$  is an integer from 1 to 4 inclusive,
  - $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 5- A compound of formula (I) according to Claim 1 characterized in that:

$R_1$  represents a group selected from:

- hydrogen, amino,
- $(C_1-C_6)$ alkyl,  $(C_3-C_6)$ alkenyl,  $(C_3-C_6)$ alkynyl, mono $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, di $(C_1-C_6)$ alkylamino $(C_1-C_6)$ alkyl, aryl, aryl $(C_1-C_6)$ alkyl, heterocycle, and 3- to 6-membered cycloalkyl $(C_1-C_6)$ alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino,  $(C_1-C_6)$ alkyl, cyano, halo $(C_1-C_6)$ alkyl,  $C(=O)OR_4$ ,  $OR_4$  and  $SR_4$ , in which  $R_4$  represents hydrogen or  $(C_1-C_6)$ alkyl,

- $W$  represents an oxygen atom, a sulphur atom, or a group  $=N-R'$ , in which  $R'$  represents  $(C_1-C_6)$ alkyl, hydroxyl, or cyano,

$X_1$  represents a nitrogen atom or a group  $-C-R_6$  in which  $R_6$  represents a hydrogen atom,  $X_2$  and  $X_3$  represent, independently of each other, a group  $-C-R_6$  in which  $R_6$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, amino, hydroxyl and halogen,



Y represents an oxygen atom,

Z represents an oxygen atom, or a group  $-NR_7$  in which  $R_7$  represents a group selected from hydrogen, and  $(C_1-C_6)$ alkyl,

n is an integer from 1 to 6 inclusive,

- 5  $Z_1$  represents  $-CR_8R_9$  wherein  $R_8$  and  $R_9$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl and hydroxyl, and
- when n is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains one or more multiple bonds,
  - or one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an
- 10 oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl;

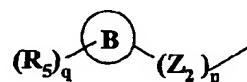
- 15 m is an integer from 0 to 3 inclusive,

the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- 20
- $X_5$  represents O, S or NH,
  - k is an integer from 0 to 3 inclusive,
  - $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
  - $X_4$  represents  $-CH_2-$ , or an oxygen atom,

- $R_{12}$  represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

$R_3$  represents a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and the group of formula :



- 5     - in which  $p$  is an integer from 0 to 6 inclusive,
- $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and hydroxy, and
  - when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one or more multiple bonds,
- 10    • or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,
- $B$  represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl,
  - 15    1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl, and indolyl,
- $q$  is an integer from 0 to 3 inclusive,
- the group(s)  $R_5$ , which may be identical or different, is (are) selected from
  - 20     $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-X_6-R_{20}$  in which :
    - $X_7$  is S, O or NH,
    - 25    •  $k$  is an integer from 0 to 3 inclusive,
    - $k1$  is an integer from 0 to 2 inclusive,
    - $k2$  is an integer from 1 to 4 inclusive,
    - $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

- $X_6$  represents a single bond,  $-\text{CH}_2-$ , an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- $R_{20}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(\text{C}_1-\text{C}_6)$ alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

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optionally, the racemic forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable salts thereof.

10 **6-** A compound of formula (I) according to Claim 1 characterized in that:

$R_1$  represents a group selected from hydrogen, mono $(\text{C}_1-\text{C}_6)$ alkylamino $(\text{C}_1-\text{C}_6)$ alkyl, di $(\text{C}_1-\text{C}_6)$ alkylamino $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_1-\text{C}_6)$ alkyl,  $(\text{C}_3-\text{C}_6)$ alkenyl,  $(\text{C}_3-\text{C}_6)$ alkynyl, aryl, aryl $(\text{C}_1-\text{C}_6)$ alkyl, and 3- to 6-membered cycloalkyl $(\text{C}_1-\text{C}_6)$ alkyl,

$W$  represents an oxygen atom, or a sulphur atom,

15  $X_1$  represents a nitrogen atom or a  $-\text{CH}$  group,

$X_2$  and  $X_3$  represent a  $-\text{CH}$  group,

$Y$  represents a group selected from oxygen atom, sulphur atom,  $-\text{NH}$ , and  $-\text{N}(\text{C}_1-\text{C}_6)$ alkyl,

$Z$  represents an oxygen atom or a  $-\text{NH}$  group,

$n$  is an integer from 1 to 3 inclusive,

20  $Z_1$  represents  $-\text{CR}_8\text{R}_9$  wherein  $R_8$  and  $R_9$ , independently of each other, represent a group selected from hydrogen,  $(\text{C}_1-\text{C}_6)$ alkyl and hydroxy, and

- when  $n$  is greater than or equal to 2, the hydrocarbon chain  $Z_1$  optionally contains one double bond,

• or one of the carbon atoms in the hydrocarbon chain  $Z_1$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a  $-NH$  group,

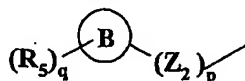
A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

m is an integer from 0 to 3 inclusive,

the group(s)  $R_2$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NR_{10}R_{11}$ ,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-SO_2R_{10}$ ,  $-(CH_2)_kSO_2NR_{10}R_{11}$ ,  $-X_5(CH_2)_kC(=O)OR_{10}$ ,  $-(CH_2)_kC(=O)OR_{10}$ ,  $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$ ,  $-(CH_2)_kC(=O)NR_{10}R_{11}$ , and  $-X_4-R_{12}$  in which:

- $X_5$  represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,
- $X_4$  represents  $-CH_2-$ , or an oxygen atom,
- $R_{12}$  represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, and hydroxyl,

$R_3$  represents a group selected from methyl and the group of formula :



- in which p is an integer from 0 to 3 inclusive,
- $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen,  $(C_1-C_6)$ alkyl, and hydroxy, and
- when p is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one double bond,

- or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,
- 5 - B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- q is an integer from 0 to 3 inclusive,
- the group(s)  $R_5$ , which may be identical or different, is (are) selected from
- 10  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ ,  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-X_6-R_{20}$  in which :
- 15 •  $X_7$  is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- $k_1$  is an integer from 0 to 2 inclusive,
- $k_2$  is an integer from 1 to 4 inclusive,
- $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen
- 20 and  $(C_1-C_6)$ alkyl,
- $X_6$  represents a single bond,  $CH_2$ , an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- $R_{20}$  represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups,
- 25 which may be identical or different, selected from  $(C_1-C_6)$ alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

30 7- A compound of formula (I) according to Claim 1 characterized in that:

R<sub>1</sub> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)alkenyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, 3- to 6-membered cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl,

W represents an oxygen atom,

X<sub>1</sub> represents -CH group or nitrogen atom, and X<sub>2</sub> and X<sub>3</sub> represent each -CH group;

5 Y represents an oxygen atom,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

Z<sub>1</sub> represents -CR<sub>8</sub>R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub>, independently of each other, represent a group selected from hydrogen and methyl, and

- 10
- when n is greater than or equal to 2, the hydrocarbon chain Z<sub>1</sub> optionally contains one double bond,
  - or one of the carbon atoms in the hydrocarbon chain Z<sub>1</sub> may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a -NH group,

15 A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

m is an integer from 0 to 3 inclusive,

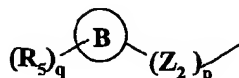
the group(s) R<sub>2</sub>, which may be identical or different, is (are) selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NR<sub>10</sub>R<sub>11</sub>, -OR<sub>10</sub>, -SR<sub>10</sub>, -SO<sub>2</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>,

20 -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>10</sub>, -X<sub>5</sub>(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, and -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>10</sub>R<sub>11</sub>, in which:

- X<sub>5</sub> represents O, S or NH,
- k is an integer from 0 to 3 inclusive,

- $R_{10}$  and  $R_{11}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

$R_3$  represents the group of formula :



- 5     - in which  $p$  is an integer from 0 to 3 inclusive,
- $Z_2$  represents  $-CR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$ , independently of each other, represent a group selected from hydrogen, and methyl, and
  - when  $p$  is greater than or equal to 2, the hydrocarbon chain  $Z_2$  optionally contains one double bond,
- 10    • or one of the carbon atoms in the hydrocarbon chain  $Z_2$  may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a  $(C_1-C_6)$ alkyl,
- $B$  represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and
  - 15    1,3-benzodioxolyl,
  - $q$  is an integer from 0 to 3 inclusive,
  - the group(s)  $R_5$ , which may be identical or different, is (are) selected from  $(C_1-C_6)$ alkyl, halogen, CN,  $NO_2$ ,  $CF_3$ ,  $OCF_3$ ,  $-(CH_2)_kNR_{15}R_{16}$ ,  $-N(R_{15})C(=O)R_{16}$ ,  $-N(R_{15})C(=O)OR_{16}$ ,  $-N(R_{15})SO_2R_{16}$ ,  $-N(SO_2R_{15})_2$ ,  $-OR_{15}$ ,  $-S(O)_{k1}R_{15}$ ,  $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$ ,  $-(CH_2)_kSO_2NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)OR_{15}$ ,  $-(CH_2)_kC(=O)OR_{15}$ ,  $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$ ,  $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$ , and  $-(CH_2)_kC(=O)NR_{15}R_{16}$ , in which :
    - $X_7$  is S, O or NH,
    - $k$  is an integer from 0 to 3 inclusive,
    - 25    •  $k_1$  is an integer from 0 to 2 inclusive,
    - $k_2$  is an integer from 1 to 4 inclusive,
    - $R_{15}$ ,  $R_{16}$  and  $R_{17}$ , which may be identical or different, are selected from hydrogen and  $(C_1-C_6)$ alkyl,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 5 **8-** A compound of formula (I) according to Claim 1 characterized in that R<sub>1</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl group, optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 9-** A compound of formula (I) according to Claim 1 characterized in that :  
W represents an oxygen atom,  
Y represents an oxygen atom,  
Z represents a NH group,  
10 Z<sub>1</sub> represents a methylene group,  
and n is equal to one,  
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 10-** A compound of formula (I) according to Claim 1 characterized in that :  
15 X<sub>1</sub> represents a -CH group or a nitrogen atom,  
and X<sub>2</sub> and X<sub>3</sub> represent each a -CH group,  
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 11-** A compound of formula (I) according to Claim 1 characterized in that :  
20 X<sub>1</sub> and X<sub>3</sub> represent each a -CH group,  
and X<sub>2</sub> represents a -CH group or a nitrogen atom,  
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

- 12-** A compound of formula (I) according to Claim 1 characterized in that :  
25 X<sub>1</sub> and X<sub>3</sub> represent each a -CH group,  
and X<sub>2</sub> represents a nitrogen atom,



optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

**13-** A compound of formula (I) according to Claim 1 characterized in that :

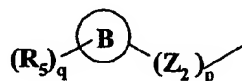
A represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

m is equal to 0 or 1,

and R<sub>2</sub> represents a group selected from (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, halogen, and (C<sub>1</sub>-C<sub>6</sub>)thioalkoxy,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

**14-** A compound of formula (I) according to Claim 1 characterized in that R<sub>3</sub> represents a group of formula :



in which:

p is equal to 1,

Z<sub>2</sub> represents a methylen group,

B represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

q is an integer from 0 to 2 inclusive,

and R<sub>5</sub> represent(s) a group selected from halogen, CN, -(CH<sub>2</sub>)<sub>k</sub>NR<sub>15</sub>R<sub>16</sub>, -S(O)<sub>k1</sub>R<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>SO<sub>2</sub>NR<sub>15</sub>R<sub>16</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)OR<sub>15</sub>, -(CH<sub>2</sub>)<sub>k</sub>C(=O)NR<sub>15</sub>R<sub>16</sub>, and -X<sub>6</sub>-R<sub>20</sub>, in which :

- k is an integer from 0 to 1 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- R<sub>15</sub> and R<sub>16</sub>, which may be identical or different, are selected from hydrogen and (C<sub>1</sub>-C<sub>6</sub>)alkyl,

- X<sub>6</sub> represents a bond,

- R<sub>20</sub> represents a 5-membered heterocyclic ring comprising from 3 to 4 heteroatoms selected from oxygen and nitrogen and optionally substituted with a methyl group or an oxo group,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

**15-** A compound of formula (I) according to Claim 1, which is:

- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
- 5 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl) amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-thienylmethyl) amide,
- 10 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (3-pyridylmethyl) amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzyl amide,
- 15 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-chlorobenzyl amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methylbenzyl amide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 20 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide ,
- Methyl 4-({[1-(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl) methanoyl]amino}methyl)benzoate,
- 25 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy benzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide,
- 30 - 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 5 acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide,
  - 3-(1-Naphth-1-ylethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 10 - 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide ,
- 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
  - 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
- 15 - 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 20 - 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide ,
- 3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
  - 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 25 benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
  - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 30 - 3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-1-cyclopropylmethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic

- acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-1-isobutyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
  - 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 5 (benzo[1,3]dioxol-5-ylmethyl)amide,
- Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
  - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid,
- 10 - 1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
  - Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
  - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 15 - 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
  - Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro
- 20 quinazoline-6-carboxylate,
- Benzyl 1-benzyl-2,4-dioxo-3-pyrid-4-ylmethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
  - 4-Pyridylmethyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 25 - 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate
  - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate,
- 30 - 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-

- ylmethyl]-benzoic acid,
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 5 - 3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 10 - 1-Methyl-2,4-dioxo-3-prop-2-ynyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 15 - 3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 20 - 1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 25 - 3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 30 - 3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-

- carboxylic acid 4-methoxy-benzylamide,
- 3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 5 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 10 - Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-acetate,
  - 3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionate,
  - 15 - 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionic acid,
  - Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyrate,
  - 20 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyric acid,
  - Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetate,
  - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid,
  - 25 - 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 30 - 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydroquinazoline-6-

- carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 5 - 3-[4-(2-Dimethylamino-ethylsulfamoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 10 - Methyl 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
  - 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
  - (E) Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoate,
  - 15 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoic acid,
  - Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylate,
  - 20 - 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylic acid,
  - Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylate,
  - 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylic acid,
  - 25 - 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 30 - 3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-

- carboxylic acid 4-methoxy-benzylamide,
- 3-[4-(*N,N*-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-Benzofurazan-5-ylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
  - 5 carboxylic acid 4-methoxy-benzylamide,
  - 3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 10 - 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine,
  - 1-Methyl-2,4-dioxo-3-[4-(2*H*-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-
  - 15 quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 20 - 2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
  - 1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-
  - 25 quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
  - 30 - Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-



- quinazolin-3-ylmethyl]-benzoic acid,
- Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-
  - 5 quinazolin-3-ylmethyl]-benzoic acid,
  - 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide,
  - 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide,
  - 10 - 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide,
  - Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-
  - 15 ylmethyl]-benzoic acid,
  - Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
  - 20 - Methyl 4-[1-ethyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-
  - 25 ylmethyl]-benzoic acid,
  - Methyl 4-{6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
  - 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,
  - 30 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-

- quinazolin-3-ylmethyl]-benzoate,
- 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
  - 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
  - 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,
  - Methyl (4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetate,
  - (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetic acid,
  - Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
  - 4-{1-Methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,
  - Methyl {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-1-yl}-acetate,
  - {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl}-acetic acid,
  - Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
  - 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

- 4-sulfamoyl-benzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - [3-(pyridin-4-ylsulfanyl)-propyl]-amide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - 5 (4-morpholin-4-yl-butyl)-amide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - (1-benzyl-piperidin-4-yl)-amide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - 4-hydroxy-benzylamine,
  - 10 - Ethyl (4- {[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-phenoxy)-acetate,
  - (4- {[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)amino]-methyl}-phenoxy)-acetic acid,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - 15 4-dimethylcarbamoylemethoxy-benzylamide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - (3-phenyl-allyl)-amide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - 4-cyano-benzylamide,
  - 20 - 4- {[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-benzoic acid,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
  - 4-dimethylcarbamoyle-benzylamide,
  - 3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic
  - 25 acid 4-methoxy-benzylamide,
  - 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - tert-Butyl {5-[6-(4-Methoxy-benzylcarbamoyle)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate,
  - 30 - 3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid

- (1,3-benzodioxol-5-ylmethyl)-amide,
- 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
  - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
  - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
  - Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate,
  - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
  - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
  - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1*H*-quinazoline-2,4-dione,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester,
  - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester,
  - 3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1*H*-quinazoline-2,4-dione,
  - 3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 1-Methyl-2,4-dioxo-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-

- quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate,
  - 4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid,
  - Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
  - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
  - 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester,
  - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylamino-ethyl ester,
  - 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-phenyl}-acetic acid,
  - 1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
  - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
  - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
  - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide,
  - 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic

- acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
  - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
  - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
  - 4-[6-(4-Methoxy-benzylcarbonyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium,
  - 4-[6-(4-Methoxy-benzylcarbonyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium ,
  - 4-[6-(4-Methoxy-benzylcarbonyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium ,
  - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
  - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
  - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
  - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide,
  - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic

- acid 3-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
  - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
  - 5     - tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate,
  - 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid,
  - 10    - 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione,
  - 3-Benzyl-1-methyl-6-phenylmethanesulfinyl-1H-quinazoline-2,4-dione,
  - 3-Benzyl-1-methyl-6-phenylmethanesulfonyl-1H-quinazoline-2,4-dione,
  - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid tert-butoxycarbonylmethyl ester,
  - 15    - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-dimethyl-propyl ester,
  - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-methyl-propyl ester,
  - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-dimethylamino-ethyl ester,
  - 20    - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid chloromethyl ester,
  - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-tert-butoxycarbonylamino-3-methyl-1-butanoyloxymethyl ester,
  - 25    - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-amino-3-methyl-butanoyloxymethyl ester hydrochloride,
  - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester,
  - 30    - and 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester.

**16-** A compound of formula (I) according to Claim 1 which is:

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
- 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt,
- Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate,
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide,
- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,
- 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide,
- 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,



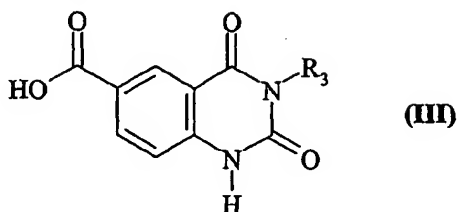
- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
- 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 5 - 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*]-
- 10 quinazolin-3-ylmethyl]-benzoic acid,
- 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid,
- 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate,
- 15 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-
- 20 tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 25 - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- Benzo[1,3]dioxol-5-ylmethyl-3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 30 (benzo[1,3]dioxol-5-ylmethyl)amide,
- 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,

- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
- 5 - Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide ,
- 1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-
- 10 tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide,
- 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 15 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
- 1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
- 20 carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
- 25 - 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
- 30 carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 5 - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,
- 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine,
- 10 - 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 15 - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,
- 20 - Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 25 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 30 - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid,

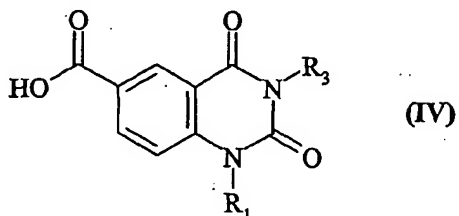
- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetic acid,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid  
4-methoxybenzylamide,
- 5 - Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetate,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid  
10 (benzo[1,3]dioxol-5-ylmethyl)amide,
- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
- 15 - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-  
20 pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid,
- 25 - 3-[4-(*N*-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-  
30 quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- and 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide.

17-Intermediate compound of formula (III):



in which R<sub>3</sub> is as defined in the compound of formula (I).

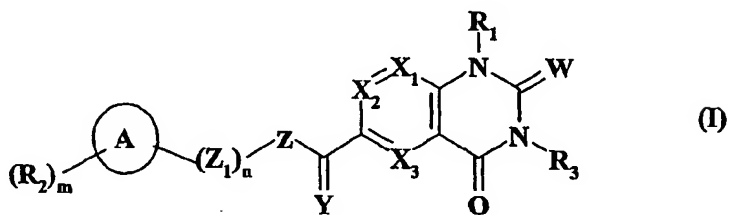
18-Intermediate compound of formula (IV):



5

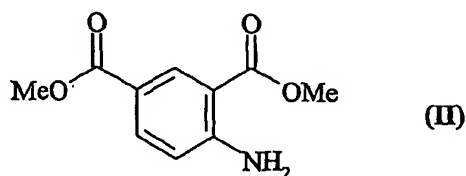
in which R<sub>1</sub> et R<sub>3</sub> are as defined in the compound of formula (I).

19- Process for manufacturing a compound of general formula (I):



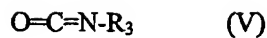
10 in which R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, A, n and m are as defined in Claim 1, R<sub>1</sub> is H, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, Y is O, Z is N-R<sub>7</sub> and W is O,

the said process being characterized in that it comprises the reaction of a compound of formula (II):



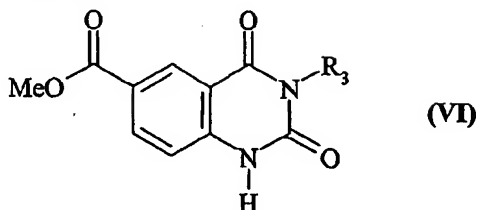
with pyridine and the compound of general formula (V):

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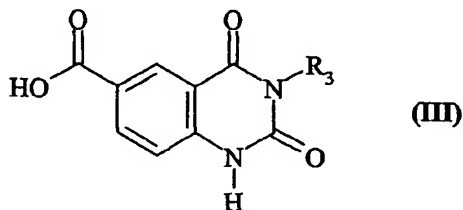
in which  $\text{R}_3$  is as defined in Claim 1,

to give the compound of general formula (VI):

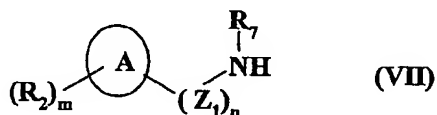


5 in which  $\text{R}_3$  is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which  $\text{R}_3$  is as defined hereinbefore:



10 the said compound of general formula (III) is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII):

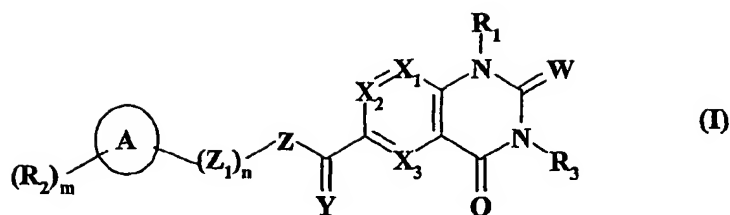


in which  $\text{R}_7$  is selected from hydrogen,  $(\text{C}_1\text{-C}_6)$ alkyl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A,  $\text{R}_2$ ,  $\text{Z}_1$ , m and n are as defined in Claim 1,

15 to give the compound of general formula (I) in which  $\text{R}_1$  represents hydrogen,  $\text{X}_1$ ,  $\text{X}_2$  and  $\text{X}_3$  are CH, Y is O, Z is N- $\text{R}_7$ , W is O, and A,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{Z}_1$ , m and n are as defined hereinbefore.

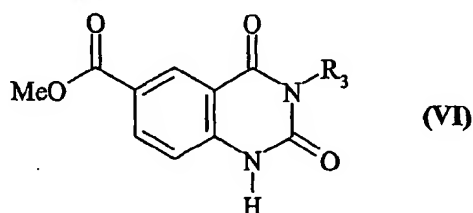
**20-** Process for manufacturing a compound of general formula (I):

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in which  $R_1$ ,  $R_2$ ,  $R_3$ ,  $A$ ,  $Z_1$ ,  $m$  and  $n$  are as defined in Claim 1,  $X_1$ ,  $X_2$  and  $X_3$  are CH,  $W$  is O,  $Y$  is O and  $Z$  is N- $R_7$ ,

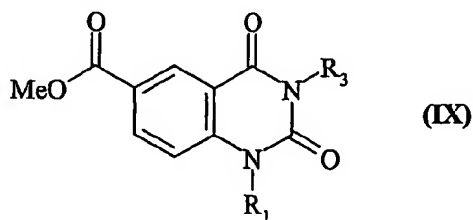
the said process being characterized in that a compound of general formula (VI):



5

in which  $R_3$  is as defined in Claim 1,

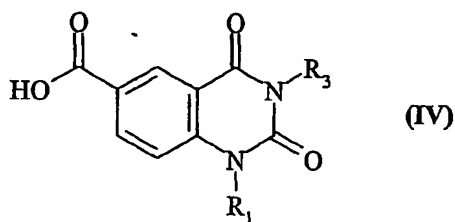
is reacted, in the presence of a base, with compound (VIII) of general formula X- $R_1$ , in which  $R_1$  is as defined in Claim 1 and  $X$  is a leaving group such as halogen, to give the compound of general formula (IX):



10

in which  $R_1$  and  $R_3$  are as defined hereinbefore,

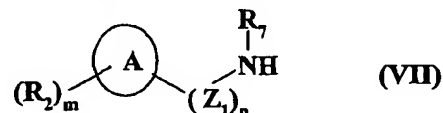
said compound of general formula (IX) is reacted in the presence of LiOH to give the compound of general formula (IV):



15

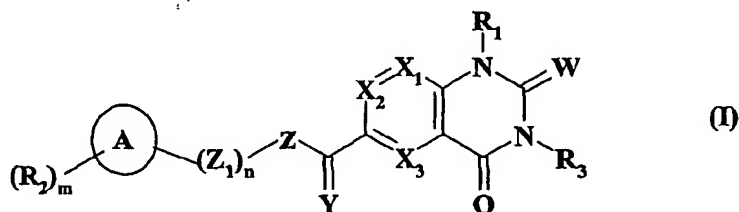
in which  $R_1$  and  $R_3$  are as defined hereinbefore,

said compound of general formula (IV) is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII):



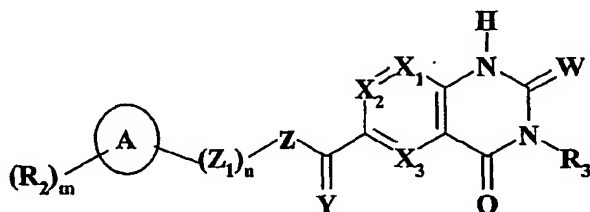
in which R<sub>7</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A, R<sub>2</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention,

to give the compound of general formula (I):



in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, A, Z<sub>1</sub>, m and n are as defined in the Claim 1, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, W is O, Y is O and Z is N-R<sub>7</sub>.

**21-** Process for manufacturing the compound of general formula (I) in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, W, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, A, Z<sub>1</sub>, m and n are as defined in Claim 1, Y is O and Z is N-R<sub>7</sub>, characterized in that a compound of general formula (I):

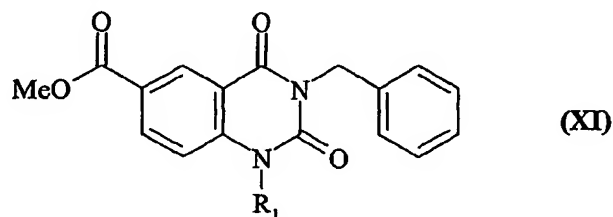


in which R<sub>1</sub> is H, and R<sub>2</sub>, R<sub>3</sub>, W, Y, Z, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, A, Z<sub>1</sub>, m and n are as defined hereinbefore,

is reacted, in the presence of a base, with a compound (VIII) of general formula X-R<sub>1</sub>, in which R<sub>1</sub> is as defined in Claim 1 and X is a leaving group such as halogen, to give the compound of general formula (I) in which R<sub>1</sub> is as defined in Claim 1.

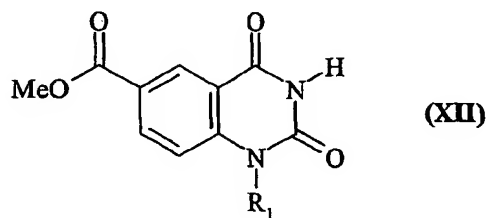


22- Process for manufacturing a compound of general formula (I) in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O, Z is N- $R_7$ ,  $R_3$  is H, and  $R_1$ ,  $R_2$ , A,  $Z_1$ , m and n are as defined in Claim 1 characterized in that a compound of general formula (XI):



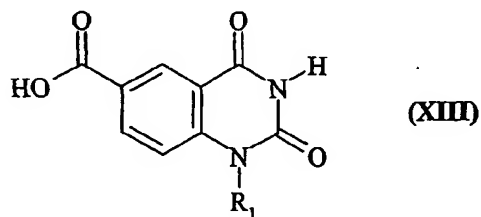
5 in which  $R_1$  is as defined hereinbefore,

is reacted with  $AlCl_3$  in a solvent such as benzene, to give the compound of general formula (XII):



in which  $R_1$  is as defined hereinbefore,

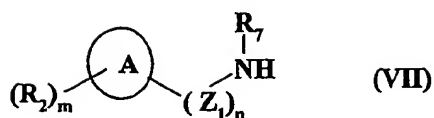
10 said compound of general formula (XII) is reacted in the presence of LiOH and a mixture of dioxane/ $H_2O$  to give the compound of general formula (XIII):



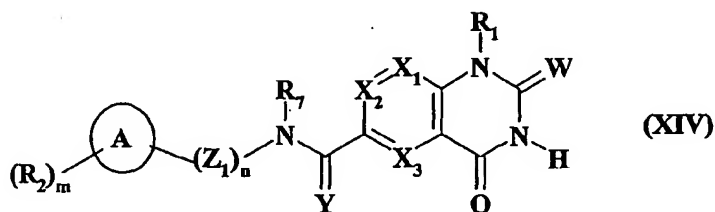
in which  $R_1$  is as defined hereinbefore,

15 said compound of general formula (XIII) is reacted, in the presence of an acid activator such as TOTU with the compound of general formula (VII):

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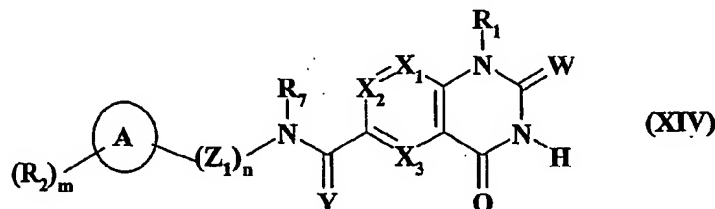
in which  $R_7$  is selected from hydrogen,  $(C_1-C_6)$ alkyl, aryl $(C_1-C_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and  $A$ ,  $R_2$ ,  $Z_1$ ,  $m$  and  $n$  are as defined in Claim 1, to give the compound of general formula (XIV):



5

in which  $X_1$ ,  $X_2$  and  $X_3$  are CH,  $W$  is O,  $Y$  is O, and  $R_7$ ,  $A$ ,  $R_2$ ,  $R_1$ ,  $Z_1$ ,  $m$  and  $n$  are as defined hereinbefore.

**23**-The process for manufacturing a compound of general formula (I) characterized in that it comprises a step in which the compound of general formula (XIV):

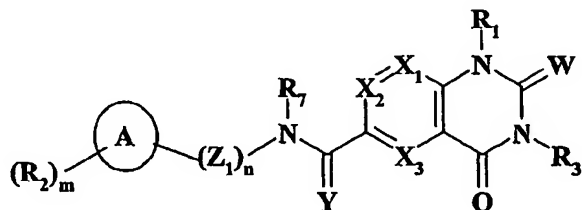


10

in which  $X_1$ ,  $X_2$  and  $X_3$  are CH,  $W$  is O,  $Y$  is O, and  $R_7$ ,  $A$ ,  $R_2$ ,  $R_1$ ,  $Z_1$ ,  $m$  and  $n$  are as defined in Claim 1,

is reacted with compound (XV) of general formula  $X-R_3$ , in which  $R_3$  is as defined in Claim 1 and  $X$  is a leaving group such as halogen,

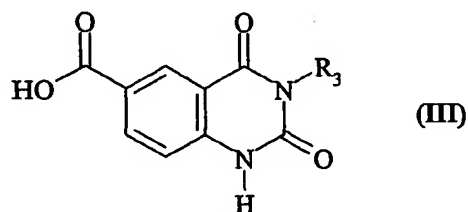
15 to give the compound of general formula (I):



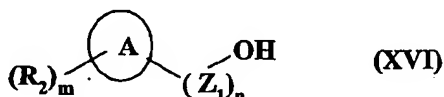
245

in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O, and  $R_7$ , A,  $R_2$ ,  $R_3$ ,  $R_1$ ,  $Z_1$ , m and n are as defined in Claim 1,

- 24- Process for manufacturing a compound of general formula (I) in which  $X_1$ ,  $X_2$  and  $X_3$  are CH, W is O, Y is O and Z is O, characterized in that a compound of general formula (III):

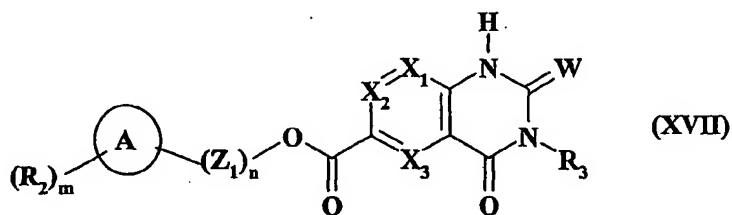


in which  $R_3$  is as defined in Claim 1,  
is reacted with a compound of general formula (XVI):



- 10 in which A,  $R_2$ ,  $Z_1$ , m and n are as defined in Claim 1,

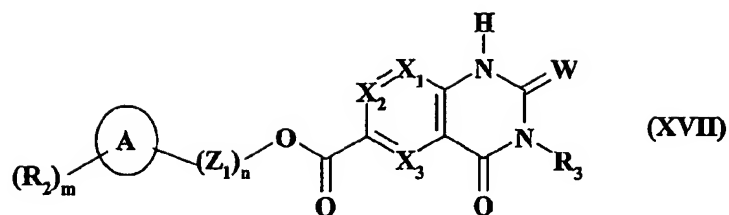
to give a compound of general formula (XVII):



in which A,  $R_2$ ,  $R_3$ ,  $Z_1$ , m and n are as defined hereinbefore,  $X_1$ ,  $X_2$  and  $X_3$  are CH, and W is O.

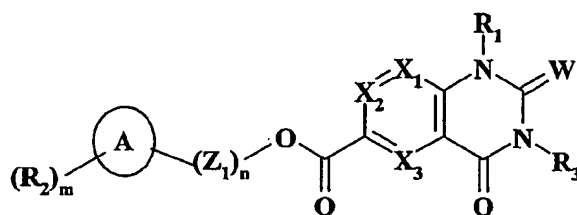
- 15 25- Process for manufacturing a compound of general formula (I), the said process is characterized in that the compound of formula (XVII) :

246



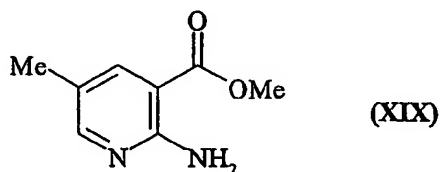
in which A, R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, m and n are as defined in Claim 1, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH; and W is O,

is reacted, in the presence of a base, with compound (VIII) of general formula X-R<sub>1</sub>, in which R<sub>1</sub> is as defined in Claim 1 and X is a leaving group such as halogen,  
5 to give the compound of general formula (I) :



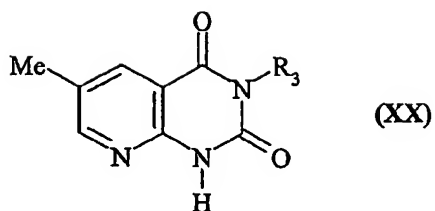
in which A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, m and n are as defined in hereinbefore, X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are CH, and W is O.

10 **26-** Process for manufacturing a compound of general formula (I) in which X<sub>2</sub> and X<sub>3</sub> are CH, X<sub>1</sub> is N, Z is O, Y is O, R<sub>1</sub> is H, W is O, and A, R<sub>2</sub>, R<sub>3</sub>, Z<sub>1</sub>, m and n are as defined in Claim 1,  
characterized in that the said process comprises a step in which a compound of general formula (XIX):



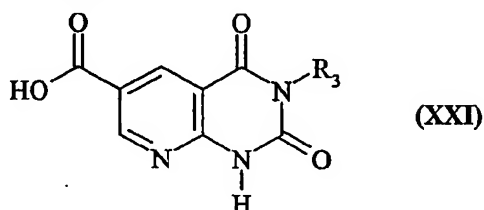
15 is reacted with pyridine and a compound (V) of general formula O=C=N-R<sub>3</sub> in which R<sub>3</sub> is as defined in Claim 1,  
to give a compound of general formula (XX):

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in which R<sub>3</sub> is as defined hereinbefore,

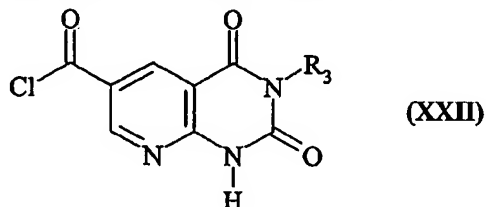
said compound of general formula (XX) is reacted in the presence of KMnO<sub>4</sub> to give the compound of general formula (XXI):



5

in which R<sub>3</sub> is as defined hereinbefore,

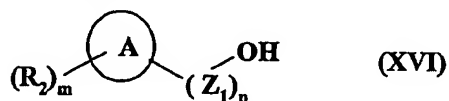
said compound of general formula (XXI) is reacted in the presence of SOCl<sub>2</sub> and optionally of a solvent to give the compound of general formula (XXII):



10

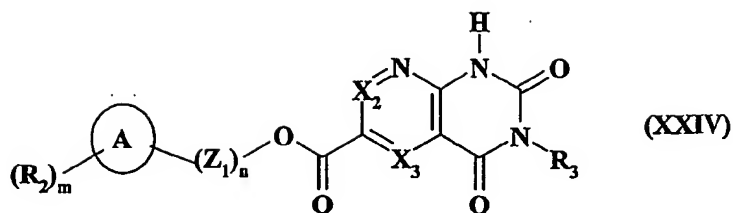
in which R<sub>3</sub> is as defined hereinbefore,

said compound of formula (XXII) is reacted with the compound of general formula (XVI):



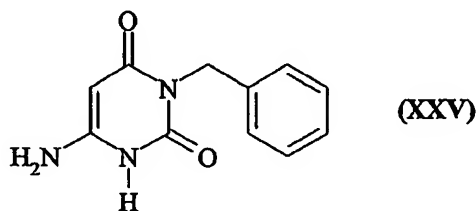
in which A, R<sub>2</sub>, Z<sub>1</sub>, n and m are as defined in Claim 1,  
to give the compound of general formula (XXIV) :

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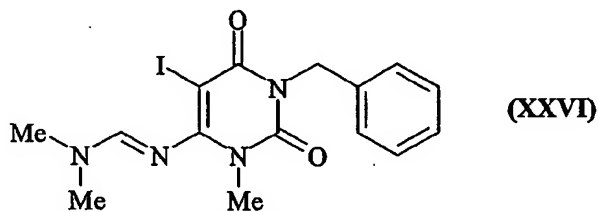


in which  $X_2$  and  $X_3$  are CH and A, n, m,  $Z_1$ ,  $R_2$  and  $R_3$  are as defined hereinbefore.

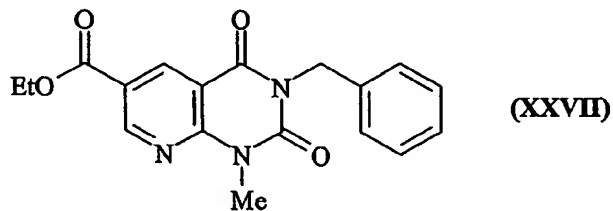
- 27- A process for manufacturing a compound of general formula (I) in which  $X_2$  and  $X_3$  are CH,  $X_1$  is N, Z is  $-NR_7$  in which  $R_7$  is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXV):



- is reacted in a first step with N,N'-dimethylformamide dimethyl acetal under reflux of DMF, and in a second step with N-iodosuccinimide, to give a compound of formula (XXVI):

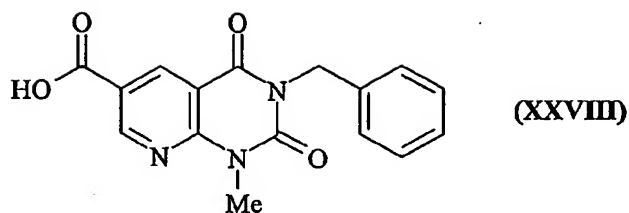


followed by reacting the compound of formula (XXVI) with ethyl acrylate in the presence of palladium diacetate, CuI and a base, to give the compound of general formula (XXVII):



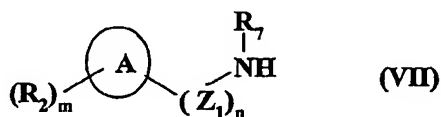
- followed by reacting the compound of formula (XXVII) in the presence of LiOH to give the compound of general formula (XXVIII):

249

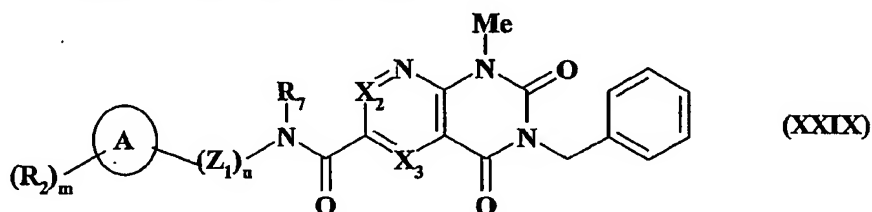


the said compound of formula (XXVIII) :

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):

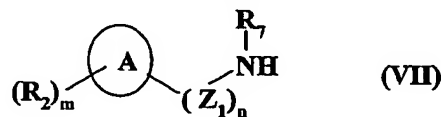


in which R<sub>7</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A, R<sub>2</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention, to give the compound of general formula (XXIX):



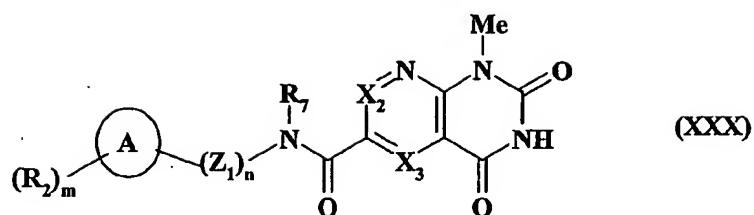
in which A, R<sub>2</sub>, R<sub>7</sub>, Z<sub>1</sub>, m and n are as defined hereinbefore, and X<sub>2</sub> and X<sub>3</sub> represents each -CH group,

- or is reacted in a first step with AlCl<sub>3</sub> in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):



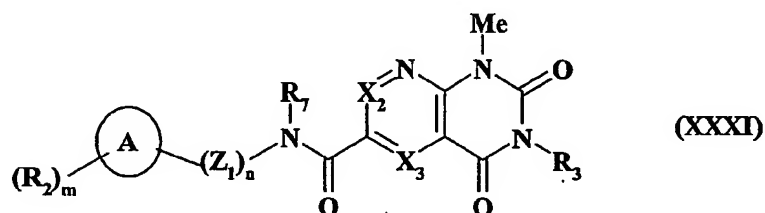
in which R<sub>7</sub> is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A, R<sub>2</sub>, Z<sub>1</sub>, m and n are as defined in the summary of the invention, to give the compound of general formula (XXX):

250



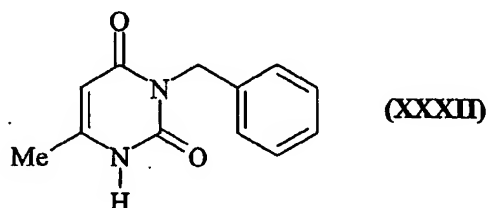
in which A, R<sub>2</sub>, R<sub>7</sub>, Z<sub>1</sub>, m and n are as defined hereinbefore, and X<sub>2</sub> and X<sub>3</sub> represents each -CH group,

5 followed by reacting the compound of formula (XXX) with a compound of formula R<sub>3</sub>-X in which R<sub>3</sub> is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXI):



28- A process for manufacturing a compound of general formula (I) in which X<sub>1</sub> and X<sub>3</sub> are CH, X<sub>2</sub> is N, Z is -NR<sub>7</sub> in which R<sub>7</sub> is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXXII):

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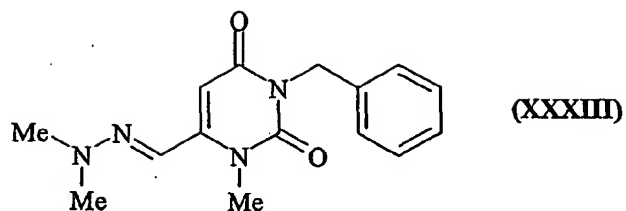


is reacted in a first step with selenium dioxide in the presence of acetic acid, in a second step with dimethylhydrazine, and in a third step with N,N'-dimethylformamide dimethylacetal under reflux of DMF, to give a compound of formula (XXXIII):

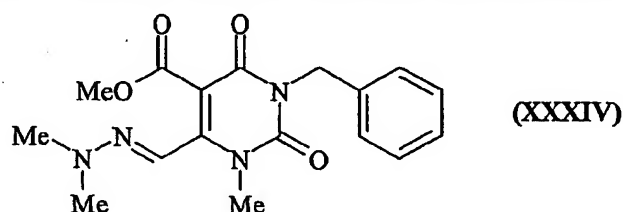
15



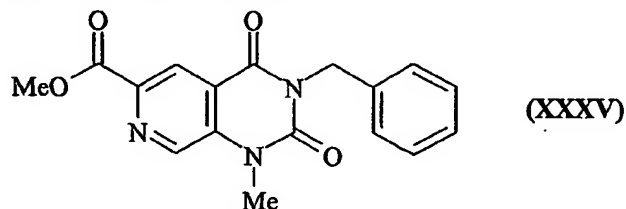
251



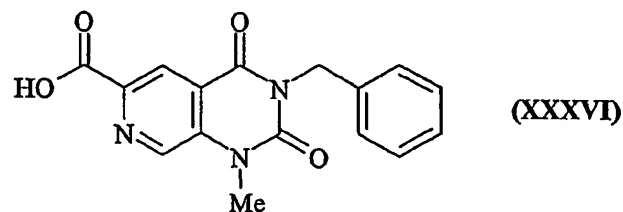
followed by reacting the compound of formula (XXXIII) with methyl acrylate in the presence of palladium diacetate, to give the compound of general formula (XXXIV):



- 5 followed by reacting the compound of formula (XXXIV) with chlorobenzene and acetic acid to give the compound of formula (XXXV):



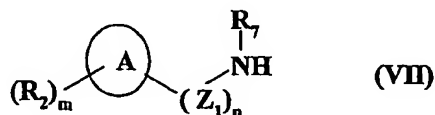
followed by reacting the compound of formula (XXXV) in the presence of a base to give the compound of general formula (XXXVI):



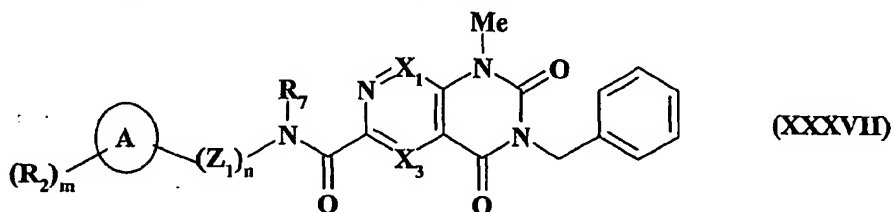
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the said compound of formula (XXXVI):

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):

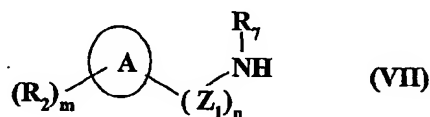


in which  $R_7$  is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A,  $R_2$ ,  $Z_1$ , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVII):

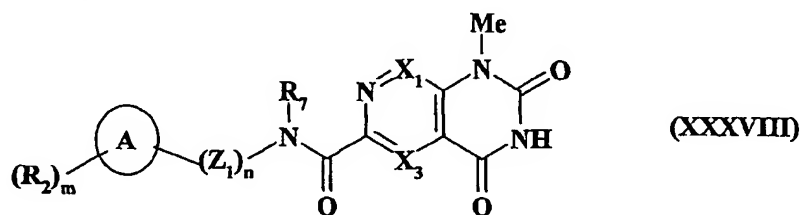


- 5 in which A,  $R_2$ ,  $R_7$ ,  $Z_1$ , m and n are as defined hereinbefore, and  $X_1$  and  $X_3$  represents each -CH group,

- or is reacted in a first step with  $AlCl_3$  in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):

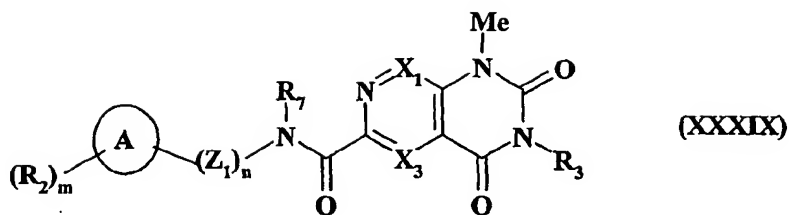


- 10 in which  $R_7$  is selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, cycloalkyl, aryl and heteroaryl, and A,  $R_2$ ,  $Z_1$ , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVIII):



- 15 in which A,  $R_2$ ,  $R_7$ ,  $Z_1$ , m and n are as defined hereinbefore, and  $X_1$  and  $X_3$  represents each -CH group,

followed by reacting the compound of formula (XXXVIII) with a compound of formula  $R_3-X$  in which  $R_3$  is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXIX):



**29-** Pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 and a pharmaceutically acceptable excipient.

**30-** Use of a compound according to any one of Claims 1 to 16, for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of type-13 matrix metalloprotease.

**31-** Use according to Claim 30, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers.

**32-** Use according to Claim 31, characterized in that the disease is arthritis.

**33-** Use according to Claim 31, characterized in that the disease is osteoarthritis.

**34-** Use according to Claim 31, characterized in that the disease is rheumatoid arthritis.

**35-** A method for treating a disease or complaint involving a therapy by inhibition of MMP-13, the said method comprising the administration of an effective amount of a compound according to any one of Claims 1 to 16 to a patient.

**36-** A method for treating according to Claim 35 characterized in that the disease or the complaint are selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis,

periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers.

5 **37-** A method for treating according to Claim 35 characterized in that the disease is arthritis.

**38-** A method for treating according to Claim 35 characterized in that the disease is osteoarthritis.

**39-** A method for treating according to Claim 40 characterized in that the disease is rheumatoid arthritis.

## INTERNATIONAL SEARCH REPORT

 In  
 of Application No  
 PCT/EP 02/01979

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>			
IPC 7	C07D239/96	C07D401/12	C07D405/12
	C07D409/14	C07D471/04	C07D403/12
	C07D413/10	C07D401/06	A61K31/5025
			A61K31/505
According to International Patent Classification (IPC) or to both national classification and IPC			
<b>B. FIELDS SEARCHED</b>			
Minimum documentation searched (classification system followed by classification symbols)			
IPC 7 C07D A61K			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched			
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)			
WPI Data, PAJ, BEILSTEIN Data, EPO-Internal, CHEM ABS Data			
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>			
Category *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
X	LIVERTON N J ET AL: "Nonpeptide glycoprotein Iib/IIIa inhibitors: substituted quinazolinones and quinazolinones as potent fibrinogen receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 5, 3 March 1998 (1998-03-03), pages 483-486, XP004136889 ISSN: 0960-894X see compound 7 page 481		17,18
X	H OGAWA ET AL: "Studies on positive inotropic agents V" CHEM PHARM BULL, vol. 36, no. 6, 1988, pages 2253-2258, XP001080174 see compound X chart I		17,18
-/-			
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.	
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family			
Date of the actual completion of the international search		Date of mailing of the international search report	
4 June 2002		25/06/2002	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer  Scruton-Evans, I	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/01979

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 <sup>3</sup>/(C07D471/04, 239:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002201020 ORDER NO A1240/0056923 & "SCREENING COLLECTION" 28 March 2000 (2000-03-28), ZELINSKY INSTITUTE OF ORGANIC CHEMISTRY, 47 LENINSKY PROSPECT, MOSCOW, 117913 RUSSIA  — —/—	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A' document defining the general state of the art which is not considered to be of particular relevance
- \*E' earlier document but published on or after the international filing date
- \*L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O' document referring to an oral disclosure, use, exhibition or other means
- \*P' document published prior to the international filing date but later than the priority date claimed

\*T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&' document member of the same patent family

Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

Name and mailing address of the ISA

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Authorized officer

Scruton-Evans, I

## INTERNATIONAL SEARCH REPORT

 Int      nal Application No  
 PCT/EP 02/01979

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002201021 ORDER NOS CHS 1938401 CHS 1938397 CHS 1938395 & "CHEMSTAR PRODUCT LIST" 16 May 2001 (2001-05-16), CHEMSTAR LTD , LENINGRADSKII PROSPECT 47, OFFICE 465, MOSCOW,125167 RUSSIA ---	1
P,X	DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002201022 ORDER NOS STOCKIN-2756, A1336/0060317, STOCKIS-85693, STOCKIS-77305, STOCKIS-81043, STOCKIS-82046 & "AMBINTER:EXPLORATORY LIBRARY" 21 January 2002 (2002-01-21), AMBINTER , 46 QUAI LOUIS BLERIoT, PARIS, F-75016, FRANCE ---	1
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X	CHEMICAL ABSTRACTS, vol. 54, no. 3, 10 February 1960 (1960-02-10) Columbus, Ohio, US; abstract no. 2375e, NESTEROV: XP002201019 abstract & SU 119 879 A (NESTEROV ET AL) 21 May 1959 (1959-05-21) Compound pyrimido'5,4-d!pyrimidine-2,4(1H,3H)-dione , 6-(benzylthio)-, RN 100382-60-3 --- -/—	1

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MURATA, SHIZUAKI ET AL: "Regioselective synthesis of 6-substituted lumazines by using highly reactive lumazine 6-triflate" retrieved from STN Database accession no. 128:243870 XP002201024 abstract &amp; CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 17-22. EDITOR(S): PFLEIDERER, WOLFGANG ROKOS, HARTMUT. PUBLISHER: BLACK,  compound RN 191275-58-8</p>	1
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KIM, YEONHEE ET AL: "Side chain reactions of 6-acetyl-1,3,7-trimethylumazine" retrieved from STN Database accession no. 128:243871 XP002201025 abstract &amp; CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 41-44. EDITOR(S): PFLEIDERER, WOLFGANG ROKOS, HARTMUT. PUBLISHER: BLACK,  compound RN 109879-41-6</p>	1
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ABOU-HADEED, KHALED ET AL: "Pteridines. CVIII. Reactions of 6,7-dichloro-1,3-dimethylumazine with sulfur nucleophiles" retrieved from STN Database accession no. 126:212115 XP002201026 compound RN 188023-01-0 abstract &amp; PTERIDINES (1996), 7(4), 113-122 ,  --- -/--</p>	1



## INTERNATIONAL SEARCH REPORT

 Int'l Application No  
 PCT/EP 02/01979

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SLADOWSKA, H. ET AL: "Synthesis and properties of amides of 1-benzyl-3-methyl- and 1-butyl-3-phenyl-7-methyl-4-oxo-2-thioxo (2,4-dioxo)-1,2,3,4- tetrahydropyrido[2,3-d]pyrimidine-6-carbox ylic acids" retrieved from STN Database accession no. 107:58977 XP002201027 compounds 109493-30-3 and 109493-25-6 abstract & FARMACO, ED. SCI. (1986), 41(12), 954-63 ,	1,29
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X	DE 24 41 959 A (CIBA GEIGY AG) 13 March 1975 (1975-03-13) compound rn 56044-13-4, Piperidine,1-(1,2,3,4-tetrahydro-2,4-diox o-6-quinazolinyl)sulfonyl! --- -/--	1

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64400 A (BEMIS GUY ; VERTEX PHARMA (US); COCHRAN JOHN (US); SALITURO FRANCES) 16 December 1999 (1999-12-16) see general formula and page 5, lines 17-end ---	1-39
A	REITER L A ET AL: "Inhibition of MMP-1 and MMP-13 with phosphinic acids that exploit binding in the S2 pocket" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 2, 18 January 1999 (1999-01-18), pages 127-132, XP004152585 ISSN: 0960-894X the whole document ---	1-39
A	CHEN J M ET AL: "STRUCTURE-BASED DESIGN OF A NOVEL, POTENT, AND SELECTIVE INHIBITOR FOR MMP-13 UTILIZING NMR SPECTROSCOPY AND COMPUTER-AIDED MOLECULAR DESIGN" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 122, 2000, pages 9648-9654, XP001010185 ISSN: 0002-7863 the whole document ---	1-39
A	WO 97 43239 A (BRITTELLI DAVID R ; ZANDT MICHAEL C VAN (US); DIXON BRIAN R (US); B) 20 November 1997 (1997-11-20) the whole document -----	1-39

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/01979

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 35-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

In ☐ International Application No  
PCT/EP 02/01979

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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